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Amino and hydroxy derivatives of dibenzofuran

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NOTE TO USERS

AMINO AND HYDROXY DERIVATIVES OF DIBENZOFURAN

By

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Signature was redacted for privacy.

Head of Major Department

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Dean of Graduate College

Iowa State College

1938

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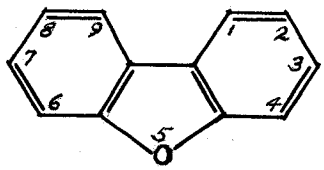
I N T R O D U C T I O N

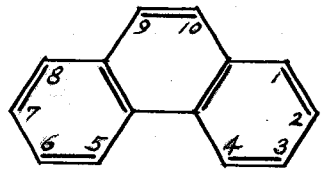
The quest, in this laboratory, for a convenient source of furantetracarboxylic acid required for orientation studies engendered the initial interest in amino and hydroxy derivatives of dibenzofuran (I) (1). While oxidative degradation methods were being applied to 2,7-diaminodibenzofuran (2), a more fruitful synthesis of furantetracarboxylic acid was devised (3), but an enduring interest in dibenzofuran chemistry had been aroused. Literature reports concerning the diaminodibenzofurans were confusing and incomplete. The hydroxydibenzofurans were rare and difficult to prepare. Structural proof for some of the most common substitution products was lacking. Urgent need for fundamental orientation studies pertaining to the dibenzofuran nucleus was made manifest.

Since the complex morphine molecule (III) (4) contains a partially reduced dibenzofuran nucleus in addition to the phenanthrene skeleton (II), the work of Eddy and collaborators (5) suggested that dibenzofuran derivatives might possess analgesic

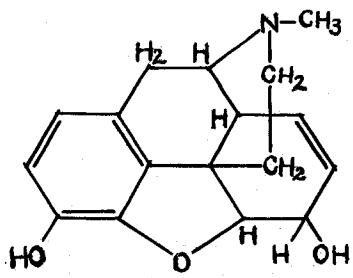
(1) Oatfield, Thesis, Iowa State College, 1933.
(2) The numbering system is in accord with the International Rules for Nomenclature /Patterson, J. Am. Chem. Soc., 47, 543, (1925)/.
(3) Gilman and Van der Wal, Rec. trav. chim., 52, 268 (1933).
(4) Gilman, "Organic Chemistry", John Wiley and Sons Inc., New York, 1938, p. 1076.
(5) Eddy, J. Pharmacol., 48, 135 (1933).



I. Dibenzofuran



II. Phenanthrene



III. Morphine

action. Furthermore, it was hoped that through physiological tests applied to various dibenzofuran derivatives, some correlations between hypnotic action and chemical constitution could be formulated (6). Such fascinating pharmacological considerations gave impetus to a thorough investigation of nuclear orientation in dibenzofuran.

Previous workers in this laboratory upon the orientation

(6) Bywater, Doctoral Dissertation, Iowa State College, 1934.

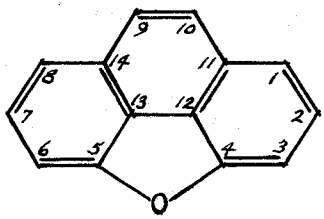
(1, 7, 8, 9) and physiological properties (6, 10, 11, 12, 13) of dibenzofuran and its derivatives have admirably reviewed the field. Part of the work carried out in this laboratory has been reported in publications, to which specific references will be given in the sequel.

Orientation studies have disclosed that all of the positions in the dibenzofuran nucleus, with the exception of the 1- and 9-positions, are vulnerable to direct nuclear substitution. An inspection of the morphine structure (III) impresses one with the necessity of being able to substitute the (so-called critical) 1-, 4-, 6-, and 9-positions of dibenzofuran in order to synthetically approach the constitution of this important alkaloid. Metalation (14, 15) proved the key to the biologically important 4- and 6-positions. VanEss (9) has unequivocally demonstrated that the bromination of 4-hydroxy- and 4-acetaminodibenzofuran involves either the 1- or 9-position. Later, Parker (13) discovered that 4-methoxydibenzofuran gives an excellent yield of

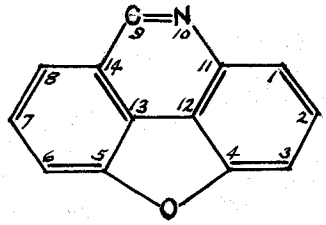
(7) Hayes, Thesis, Iowa State College, 1934.
(8) VanEss, M.W., Doctoral Dissertation, Iowa State College, 1936.
(9) VanEss, P.R., Doctoral Dissertation, Iowa State College, 1936.
(10) Kirkpatrick, Doctoral Dissertation, Iowa State College, 1935.
(11) Smith, E.W., Doctoral Dissertation, Iowa State College, 1936.
(12) Bradley, Doctoral Dissertation, Iowa State College, 1937.
(13) Parker, Doctoral Dissertation, Iowa State College, 1937.
(14) Gilman and Young, J. Am. Chem. Soc., 56, 1415 (1934).
(15) Gilman and Young, ibid., 57, 1121 (1935).

the same bromination product which VanEss obtained by methylating his bromohydroxy compound. Parker also proved that the Friedel-Crafts reaction acylates either the 1- or 9-position of 4-methoxydibenzofuran.

The objectives of this investigation were to render 4, 6-disubstituted dibenzofurans more available, to prepare certain 1, 4, 6, 9-tetrasubstituted dibenzofurans, and to explore the feasibility of synthesizing 4, 5-phenanthrylene oxide (IV) and 4, 5-phenanthridine oxide (V) derivatives through cyclization methods applied to the 1- and 9-positions of 4, 6-disubstituted dibenzofuran derivatives, e.g., 4, 6-dimethoxydibenzofuran.



IV. 4,5-Phenanthrylene Oxide



V. 4,5-Phenanthridine Oxide

Amino and hydroxy derivatives were chosen because of their inherent ability to activate the aromatic nucleus. The compounds were also to be submitted for pharmacological test (16), and a review of useful analgesics, coupled with the results of previous physiological

(16) These pharmacological tests were carried out in the laboratories of Parke, Davis and Company through the courtesy of Dr. Dox and Dr. Bywater of that company.

tests on dibenzofurans, favored the conclusion that amino and hydroxy derivatives were most apt to manifest analgesic activity.

H I S T O R I C A L

In the following tabulation, an attempt has been made to list all amino and hydroxy derivatives of dibenzofuran which have appeared in the literature to date. In addition, a number of compounds taken from unpublished work in this laboratory have been included along with the new compounds described in this thesis. All available references to each individual compound have been collected, and, for convenience, the page number has also been inserted when a general reference is involved. In some instances, the melting points of compounds appearing in the patent literature were not reported. The hydrochlorides of liquid bases have been tabulated. Because of the inordinate task of compilation, the brazans, the dinaphthylene oxides, the morphine alkaloids, and many other derivatives of fused ring systems inhering a dibenzofuran nucleus have been omitted. Chemical Abstracts has been the criterion in deciding which compounds should be included.

TABLE I.

AMINO AND HYDROXY DERIVATIVES OF DIBENZOFURAN

Name of Compound	M. P.	Reference
1-Acetaminodibenzofuran	205	(9) p. 52
1-Acetamino-3,4-dimethoxydibenzofuran	196-196.5	(17)
1-Acetamino-4,6-dimethoxydibenzofuran	244-245	(17)
1-Acetamino-4-ethoxydibenzofuran	218.5	(18)
1-Acetamino-4-methoxydibenzofuran	222-223	(13) p. 81
1-Acetamino-2-nitro-4-methoxydibenzofuran	244	(13) p. 82
2-Acetaminodibenzofuran	162-163	(19) (6) p. 33
2-Acetamino-3-bromodibenzofuran	240-241	(20) (9) p. 26 (6) pp.41, 42
2-(γ-Acetamino-n-propyl)-dibenzofuran	120	(21)
3-Acetaminodibenzofuran	178	(22)
4-Acetaminodibenzofuran	172.5	(10) p.100 (23)
2-Acetoxydibenzofuran	114-115	(24)

(17) This thesis.
(18) Unpublished work by Mr. A. L. Jacoby, this laboratory.
(19) Gilman, Bywater, and Parker, J. Am. Chem. Soc., 57, 885 (1935).
(20) Gilman, Brown, Bywater, and Kirkpatrick, J. Am. Chem. Soc., 56, 2473 (1934).
(21) Mayer and Krieger, Ber., 55, 1659 (1922).
(22) Borsche and Schacke, Ber., 56, 2498 (1923).
(23) Kirkpatrick and Parker, J. Am. Chem. Soc., 57, 1123 (1935).
(24) Unpublished work by Mr. Jack Swislowsky, this laboratory.

TABLE I (continued)

Name of Compound	M. P.	Reference
3-Acetoxydibenzofuran	111-111.5	(25)
8-Acetoxy-3,7-dimethoxydibenzofuran-1,4-dione	252-254	(26)
1-Acetyl-3,4-dimethoxydibenzofuran	90.5-91	(17)
1-Acetyl-4,6-dimethoxydibenzofuran	178.5-179.5	(17)
1-Acetyl-3,4-dimethoxydibenzofuran oxime	156-157	(17)
1-Acetyl-4,6-dimethoxydibenzofuran oxime	203-204	(17)
1-Acetyl-4-methoxydibenzofuran	132-133	(13) p. 80
1-Acetyl-4-methoxydibenzofuran oxime	176-177.5	(13) p. 80
2-Acetyl-7-acetaminodibenzofuran	203	(13) p. 99
2-Acetyl-7-acetamino-8-nitro-dibenzofuran	270-271	(13) p.100
2-Acetyl-7-aminodibenzofuran	156	(13) p. 99
1-Allyl-2-hydroxydibenzofuran	83	(9) p. 30
1-Allyl-2-methoxydibenzofuran	67-68	(9) p. 32
2-Allyloxydibenzofuran	b.p. 178-180/4mm.	(9) p. 29
1-Aminodibenzofuran	74	(9) p. 51
1-Amino-4-acetaminodibenzofuran	202	(24)

(25) Tatematsu and Kubota, Bull. Chem. Soc. Japan, 9, 448 (1934) [C. A., 29, 1091 (1935)].
(26) Erdtman, Proc. Roy. Soc. (London), A145, 223 (1934).

TABLE I (continued)

Name of Compound	M. P.	Reference
1-Amino-3,4-dimethoxydibenzofuran	162.5-163	(17)
1-Amino-4,6-dimethoxydibenzofuran	162-162.5	(17)
1-Amino-4-ethoxydibenzofuran	91	(18)
1-Amino-4-methoxydibenzofuran	104 103-104	(18) (13)
1-Amino-2-nitro-4-methoxydibenzofuran	206-207	(13) p. 83
1-Amino-1,2,3,4-tetrahydro-β(or γ)-brazan hydrochloride	266-267	(13) p. 95
2-Aminodibenzofuran	125 127-128	(27) (28) (6) p. 30 (29) (30) (10) p. 87 (12) p. 58
2-Amino-4-arsonodibenzofuran	218 (dec.)	(31)
2-Amino-3-bromodibenzofuran	172-173	(20) (9) p. 27
2-Aminodibenzofuro-[3,2-d]-thiazole	268-269	(13) p. 91
2-α-Aminoethyldibenzofuran hydrochloride	222-223	(13) p. 72
2-β-Aminoethyldibenzofuran hydrochloride	278	(10) pp.95,96
2-(2-Amino-1-hydroxy)-ethyldibenzofuran	132 (corr.)	(32)

(27) Cullinane, J. Chem. Soc., 1930, 2267.
(28) Cullinane, ibid., 1932, 2365.
(29) Brumberg, Doctoral Dissertation, Göttingen, 1925.
(30) German patent 591,213 [C. A., 28, 2366 (1934)].
(31) Hall and Hamilton, J. Am. Chem. Soc., 56, 1779 (1934).
(32) Mosettig and Robinson, ibid., 57, 2186 (1935).

TABLE I (continued)

Name of Compound	M. P.	Reference
2-Amino-4-methoxydibenzofuran	127-127.5	(13) p. 85
2-Amino-3-nitrodibenzofuran	207-209 206-208	(29) (6) p. 39
2-Amino-7-nitrodibenzofuran	143	(6) p. 55 (20)
2-(2-Amino-1-oxo)-ethyldibenzofuran hydrochloride	244-255 (corr.)(dec.)	(32)
2-(γ-Amino-n-propyl)-dibenzofuran hydrochloride	219-220	(21)
3-Aminodibenzofuran	94 94-95	(33) (28) (1)pp.15-20 (10) p. 66 (12) p. 56
3-Amino-4-acetaminodibenzofuran	236-237	(24)
3-Amino-2-dibenzofurylthiocyanate	175	(13) p. 88
3-Amino-4-methoxydibenzofuran	75.5	(18) (13) p.107
3-Amino-8-nitrodibenzofuran	268	(28)
4-Aminodibenzofuran	84.5-85.5	(6)pp.61,62 (10) p.101 (9) p. 46 (12) p. 58 (23)
4-β-Aminoethyldibenzofuran hydrochloride	263	(10) p. 98
4-Amino-6-hydroxydibenzofuran	191.5-192.5	(17)

(33) Borsche and Bothe, Ber., 41, 1940 (1908).

TABLE I (continued)

Name of Compound	M. P.	Reference
4-Amino-6-methoxydibenzofuran	109	(17)
8-Amino-3-dibenzofurylarsonic acid	above 250	(34)
3,3'-Azobisdibenzofuran	282	(22)
3,3'-Azoxybisdibenzofuran	259-260	(22)
1-Benzeneazo-4,6-dimethoxydibenzofuran	170	(17)
1-Benzeneazo-2-hydroxydibenzofuran	165.5-166	(8) p. 77
1-Benzeneazo-4-hydroxydibenzofuran	174-175	(8) p. 78
1-Benzeneazo-4-hydroxy-6-methoxy-dibenzofuran	175	(17)
2-Benzeneazo-3-hydroxydibenzofuran	177-179	(8) p. 77
Benzofuro-[2,3-f]-quinoline	106-107(corr.)	(35)
Benzofuro-[3,2-g]-quinoline	168-169(corr.)	(35)
3-Benzoylaminodibenzofuran	201	(33)
N-Benzoyl-1,2,3,4-tetrahydrobenzofuro-[2,3-f]-quinoline	158-159(corr.)	(35)
N-Benzoyl-1,2,3,4-tetrahydrobenzofuro-[3,2-g]-quinoline	198-200(corr.)	(35)
Bi-(4-dibenzofuryl)	191	(17)
Bi-(4,6-dimethoxy-1-dibenzofuroyl)	above 300	(17)

(34) Skiles and Hamilton, J. Am. Chem. Soc., 59, 1006 (1937).
(35) Mosettig and Robinson, J. Am. Chem. Soc., 57, 902 (1935).

TABLE I (continued)

Name of Compound	M. P.	Reference
Bi-(6-hydroxy-4-dibenzofuryl)	285-286	(17)
Bi-(4-methoxy-1-dibenzofuroyl)	329	(17)
Bi-(6-methoxy-4-dibenzofuryl)	237-238	(17)
2,4-Bis-(diethylaminoethylamino)-dibenzofuran	b.p.255/1mm.	(36)
3-[Bis-(diethylaminoethoxyethyl)-amino]-dibenzofuran	b.p.260-262/1mm.	(36)
3-[Bis-(diethylaminoethyl)-amino]-dibenzofuran	b.p.225/1mm.	(36)
3,7-Bis-(diethylaminoethylamino)-dibenzofuran	b.p.250-260/1mm.	(36)
3-[Bis-(N-piperidylethyl)-amino]-dibenzofuran	b.p.250-260/1mm.	(36)
1-Bromodibenzofuran	67	(9) p. 50
1-Bromo-4-acetaminodibenzofuran	228	(9) p. 48
1-Bromo-4-aminodibenzofuran	118-118.5	(9) p. 49
1-Bromo-3-amino-4-methoxydibenzofuran	135-136	(13) p.108.
1-Bromo-3,4-dimethoxydibenzofuran	108	(17)
1-Bromo-4,6-dimethoxydibenzofuran	152	(17)
1-Bromo-2-hydroxydibenzofuran	123-123.5	(9) p. 23 (8) p. 78

(36) German patent 550,327 [C. A., 26, 4062 (1932)].

TABLE I (continued)

Name of Compound	M. P.	Reference
1-Bromo-4-hydroxydibenzofuran	151.5-152	(9) pp.42,49 (8) p. 81
1-Bromo-3-hydroxy-4-methoxy-dibenzofuran	161-162	(17)
1-Bromo-2-methoxydibenzofuran	117-118	(9) p. 24
1-Bromo-4-methoxydibenzofuran	97-97.5	(13) p. 74 (9) p. 43
1-Bromo-3-nitro-4-methoxydibenzofuran	160-161	(13) p.106
2-Bromo-3-acetaminodibenzofuran	194	(10) p. 72 (20)
2-Bromo-3-aminodibenzofuran	127-128 129	(20) (10) p. 73 (6) p. 57
2-Bromo-7-aminodibenzofuran	133-134	(20) (6) p. 54
2-Bromo-3-hydroxydibenzofuran	111-112 113-113.5	(8) p. 80 (25)
3-Bromo-4-hydroxydibenzofuran*	151.5-152	(37)
4-Bromo-6-hydroxydibenzofuran	138-139	(17)
4-Bromo-6-methoxydibenzofuran	114	(17)
3-Bromopyridodibenzofuran	152	(23) (10)
1-Chloroacetyl-4-methoxydibenzofuran	165-166	(17)

* Probably 1-Bromo-4-hydroxydibenzofuran.

(37) Phatak and Leake, J. Pharmacol., 58, 157 (1936).

TABLE I (continued)

Name of Compound	M. P.	Reference
2-Chloromethyl-3-chloro-4-amino-diphenyleneoxypyridine-dibenzofuran	240-242	(38)
3-Chloroacetaminodibenzofuran	162-164	(38)
4-β-Chloroethoxydibenzofuran	64-65	(23)
2,7-Diacetaminodibenzofuran	290(dec.)	(28)
2,8-Diacetaminodibenzofuran	258	(22)
3-Diacetaminodibenzofuran	85	(33) (10) p. 67
3,7-Diacetaminodibenzofuran	322	(28)
4,6-Diacetaminodibenzofuran	297-298	(17)
2,8-Diacetoxydibenzofuran	151-151.5	(24)
3,4-Diacetoxydibenzofuran	104-105	(17)
4,6-Diacetoxydibenzofuran	177	(17)
2,3-Diaminodibenzofuran	165-166	(22) (29) (6) p. 39 (10) pp. 70,74 (20)
2,7-Diaminodibenzofuran	152	(28) (39) (27) (1) p. 24 (6) p. 55 (20)

(38) Fel'dman, J. Gen. Chem. (U.S.S.R.), 6, 1234 (1936) [C. A., 31, 1407 (1937)].

(39) Mailhe, Compt. rend., 154, 1515 (1912); Bull. soc. chim., [4] 11, 1011 (1912).

TABLE I (continued)

Name of Compound	M. P.	Reference
2,8-Diaminodibenzofuran	215	(24) (22)
3,7-Diaminodibenzofuran	150-152	(28) (64) (1) p. 11
3,7-Diamino-4,6-dimethyldibenzofuran	- - -	(65)
4,6-Diaminodibenzofuran	152	(17)
Diazomethyl 4,6-dimethoxy-1-dibenzofuryl ketone	151(dec.)	(17)
" Dibenzofuranazophenol	199	(33)
3-Dibenzofurandiazonium chloride	158-160(dec.)	(37)
Dibenzofuran-indigo	sub. above 350	(22)
" Dibenzofurantetrahydroquinoline-4-aminodibenzofuran	above 300	(38)
" 2-(3-Dibenzofurylamino)-benzoic acid	227	(22)
3-Dibenzofurylurea	222-223	(13) p. 85
1,8-Dibromo-4,6-dihydroxydibenzofuran	239-240	(17)
1,3(?)-Dibromo-4,6-dimethoxy-dibenzofuran	173.5-174	(17)
1,9-Dibromo-4,6-dimethoxydibenzofuran	167-168	(17)
1,3(?)-Dibromo-4-hydroxy-6-methoxy-dibenzofuran	177-178	(17)
Di-(4,6-dimethoxy-1-dibenzofuryl) ketone	254-255	(17)

TABLE I (continued)

Name of Compound	M. P.	Reference
1-β-Diethylaminoethyl-4-methoxy-dibenzofuran hydrochloride	187 (dec.)	(13)
2-ω-Diethylaminoacetyldibenzofuran hydrochloride	204-206	(10) p. 90 (23)
	200-212(corr.)	(32)
2-β-Diethylaminoethyldibenzofuran hydrochloride	192-193	(23)
2-∝-Diethylaminoethyldibenzofuran picrate	173-174	(13) p. 74
2-[2-(Diethylamino)-1-hydroxy]-ethyldibenzofuran hydrochloride	157-159(corr.)	(32)
	157	(23)
Diethylaminomethyl-2-dibenzofuryl-methylcarbinol hydrochloride	145	(23)
2-[2-(Diethylamino)-1-oxo]-ethyl-dibenzofuran hydrochloride	200-212(corr.)	
3-Diethylaminodibenzofuran	68	(18)
		(10) p. 81
3-(Diethylaminoethoxyethylamino)-dibenzofuran	b.p.235/1mm.	(36)
3-(Diethylaminoethylamino)-dibenzofuran	55	(36)
4-β-Diethylaminoethoxydibenzofuran hydrochloride	128.5-129.5	(23)
4-β-Diethylaminoethyldibenzofuran hydrochloride	184-185	(23)
Diethyl dibenzofuran-3-aminomalonate	100	(15)

TABLE I (continued)

Name of Compound	M. P.	Reference
1,4-Dihydro-3-aminodibenzofuran	72	(12) p. 60
1,4-Dihydrodibromo-3-aminodibenzofuran	186 (dec.)	(12) p. 60
1,4-Dihydro-4-hydroxydibenzofuran	116-117	(12) p. 78 (11) p.125
1,4-Dihydroxydibenzofuran	217-218(dec.)	(9) p. 45
2,6-Dihydroxydibenzofuran	194-195	(40)
2,7-Dihydroxydibenzofuran	192-193	(40)
2,8-Dihydroxydibenzofuran	242-243	(24) (40)
2,8-Dihydroxy-4,6-dimethyldibenzofuran	232	(65)
3,4-Dihydroxydibenzofuran	164-164.5	(17)
3,7-Dihydroxydibenzofuran	241-241.5	(41)
4,6-Dihydroxydibenzofuran	200-202 190	(17) (15)
1,2-Dimethoxydibenzofuran	79	(9) p. 37
1,4-Dimethoxydibenzofuran	78.5	(9) p. 45
2,8-Dimethoxydibenzofuran	88-89	(24)
3,4-Dimethoxydibenzofuran	60-61	(17)
3,7-Dimethoxydibenzofuran	150	(41)

(40) French patent 816,719 [C. A., 32, 2145 (1938)].
(41) Hata, Tatematsu and Kubota, Bull. Chem. Soc. Japan, 10, 425 (1935) [C. A., 30, 1056 (1936)].

TABLE I (continued)

Name of Compound	M. P.	Reference
3,4-Dimethoxy-α-(4-dibenzofuroyl-amino)-acetophenone	178-179	(13) p.105
3,4-Dimethoxy-α-(4-dibenzofuryl-acetamino)-acetophenone	186-187	(13) p.104
3,7-Dimethoxy-8-hydroxy-1,4-dibenzofurandione	242-245	(42)
4,6-Dimethoxydibenzofuran	128-129	(17)
4,6-Dimethoxy-1-dibenzofuran-carboxylic acid	297-298	(17)
4,6-Dimethoxy-1-dibenzofuryl-acetamide	210-211	(17)
4,6-Dimethoxy-1-dibenzofurylacetic acid	205-206	(17)
2-[2-(Dimethylamino)-1-hydroxy]-ethyldibenzofuran	88-89(corr.)	(32)
2-[2-(Dimethylamino)-1-hydroxy]-ethyldibenzofuran benzoic acid ester	99-100(corr.)	(32)
2-[2-(Dimethylamino)-1-oxo]-ethyl-dibenzofuran	82-83(corr.)	(32)
2-β-Dimethylaminopropionyl-dibenzofuran	88-89	(13)
2-[γ-(Dimethylamino)-n-propyl]-dibenzofuran hydrochloride	195-197(corr.)	(35)
2,8-Dimethyl-3,7-diaminodibenzofuran	- - -	(66)

(42) Erdtman, Svensk. Kem. Tids., 44, 135 (1932) [C. A., 26, 4804 (1932)].

TABLE I (continued)

Name of Compound	M. P.	Reference
3-Dimethylaminodibenzofuran	96	(23) (10) p. 79
4-[γ-(Dimethylamino)-n-propyl]-dibenzofuran hydrochloride	168-169(corr.)	(35)
1,4-Dimonoacetaminodibenzofuran	307-308	(24)
1,X-Dinitro-4-acetaminodibenzofuran	288	(24)
Dinitro-2-hydroxydibenzofuran	240 (dec.)	(18)
Dinitro-3-hydroxydibenzofuran	216-217(dec.)	(25)
3,4-Dimonoacetaminodibenzofuran	257	(24)
3,X-Dinitro-4-acetaminodibenzofuran	277-278	(24)
3,X-Dinitro-4-hydroxydibenzofuran	225 (dec.)	(18)
3,X-Dinitro-4-methoxydibenzofuran	177	(18)
1,9-Diphenyldibenzofuran	154-155	(45)
1-Ethoxalyl-4-methoxydibenzofuran	113	(17)
3-Ethoxydibenzofuran	97-97.5	(25)
2-[2-(Ethylamino)-1-hydroxy]-ethyldibenzofuran	99.5-101(corr.)	(32)
2-[2-(Ethylamino)-1-oxo]-ethyl-dibenzofuran hydrochloride	254-256(corr.)	(32)
3-Ethylaminodibenzofuran hydrochloride	above 315	(23) (10) p. 78
Ethyl dibenzofuran-indoxylate	191	(22)

(45) Sako, Bull. Chem. Soc. Japan, 9, 55 (1934) [C. A., 28, 3730 (1934)].

TABLE I (continued)

Name of Compound	M. P.	Reference
Ethyl ether of piperidinomethyl-2-dibenzofurylcarbinol hydrochloride	175	(10) p. 92
1,1',2,3,4,5'-Hexahydro-2-hydroxy-5',8-dimethyldibenzofuran	74	(44)
1,3,4,7,8,9-Hexamethoxydibenzofuran	126-127.5	(45)
3-Hydrazinodibenzofuran	152 174-175	(33) (17)
1-Hydroxydibenzofuran	138.5-140	(9) p. 52
1-β-Hydroxyethyl-4-methoxydibenzofuran	96-96.5	(15) p. 76
1-Hydroxy-2-methoxydibenzofuran	111-111.5	(9) p. 35
1-Hydroxy-4-methoxydibenzofuran	155	(9) p. 44
2-Hydroxydibenzofuran	134	(19) (46) (9) p. 22 (6) p. 36 (40) (30)
2-Hydroxy-7-acetaminodibenzofuran	242-243	(40)
2-Hydroxy-7-aminodibenzofuran	200-201	(40)
2-Hydroxy-3-bromodibenzofuran*	123-123.5	(37)

(44) Pummerer, Puttfarcken, and Schopflocker, Ber., 58, 1808 (1925).
(45) Erdtman, Ann., 513, 240 (1934).
(46) German patent 606,350 [C. A., 29, 1434 (1935)].
* Probably 1-Bromo-2-hydroxydibenzofuran.

TABLE I (continued)

Name of Compound	M. P.	Reference
2-Hydroxy-3-bromodibenzofuran	143-144	(9)
2-Hydroxy-6-chlorodibenzofuran	167-169	(47) (40)
2-Hydroxy-7-chlorodibenzofuran	167-168	(47) (40)
2-Hydroxy-8-chlorodibenzofuran	177-178	(47) (40)
2-Hydroxy-9-chlorodibenzofuran	- - -	(47)
2-Hydroxy-3-dibenzofuran-carboxylic acid	293	(48) (49) (30) (50)
2-(1-Hydroxy)-ethyldibenzofuran	63-64(corr.)	(32)
2-β-Hydroxyethyldibenzofuran	67-67.5	(23)
2-Hydroxy-7-methoxydibenzofuran	151-152	(40) (47)
2-Hydroxy-8-methoxydibenzofuran	- - -	(47)
2-Hydroxy-7-methyldibenzofuran	147-148	(40) (47)
2-Hydroxy-8-methyldibenzofuran	160-161	(40) (47)

(47) British patent 470,021 [C. A., 32, 1487 (1938)].
(48) German patent 593,506 [C. A., 28, 3422 (1934)].
(49) British patent 426,403 [C. A., 29, 5671 (1935)].
(50) U. S. patent 2,050,958 [C. A., 30, 6960 (1936)].

TABLE I (continued)

Name of Compound	M. P.	Reference
3-Hydroxydibenzofuran	138-139	(6) pp. 46,50 (25) (19) (51) (30) (52)
3-Hydroxy-2-dibenzofurancarboxylic acid	245	(30) (49)
3-(3-Hydroxy-2-naphthoyl)-amino-dibenzofuran	- - -	(53) (54)
3-Hydroxy-4-methoxydibenzofuran	109-110	(17)
4-Hydroxydibenzofuran	102	(15) (17) (6) p. 57 (9) p. 42
4-β-Hydroxyethyldibenzofuran	70-71	(23)
4-Hydroxy-6-methoxydibenzofuran	111-112	(15) (17)
8-Hydroxy-3,7-dimethoxydibenzofuran-1,4-dione	250	(26)
8-Hydroxy-3,7-dimethyldibenzofuran-1,4-dione	218-220	(26)
2-Methoxydibenzofuran	46-47	(9) p. 25

(51) Kruber, Ber., 69, 107 (1936).
(52) U. S. patent 1,997,744 [C. A., 29, 3853 (1935)].
(53) U. S. patent 1,936,926 [C. A., 28, 1054 (1934)].
(54) French patent 731,166 [C. A., 27, 1202 (1933)].

TABLE I (continued)

Name of Compound	M. P.	Reference
2-Methoxy-3-allyldibenzofuran	b.p.158-159/4mm.	(9) p. 34
2-Methoxy-3-bromodibenzofuran	171-172	(9)pp.25,29
2-Methoxy-8-bromodibenzofuran	92.5	(9) p. 39
2-Methoxy-1-dibenzofurancarboxylic acid	156-157	(9) p. 38 (55)
2-Methoxy-3-dibenzofurancarboxylic acid	206-207	(9) p. 39 (55)
3-Methoxydibenzofuran	93-94	(56)
4-Methoxydibenzofuran	52	(15) (17)
4-Methoxy-1-dibenzofurancarboxylic acid	279-280	(13)pp.75,80
4-Methoxy-1-dibenzofuryl-∝-oxo-acetic acid	187	(17)
4-Methoxy-1-dibenzofuryl-∝-oxo-acetic acid semicarbazone	211-212(dec.)	(17)
Methyl 3-acetamino-6-dibenzofuran-carboxylate	245-246	(8) p. 88
2-Methyl-8-acetyldibenzofuro-[2,3-d]-imidazole	298	(13) p.102
3-Methylaminodibenzofuran	48-49	(23) (10) p. 76
2-[2-(Methylamino)-1-oxo]-ethyl-dibenzofuran hydrochloride	225-250(corr.)	(32)

(55) Bebb, Doctoral Dissertation, Iowa State College, 1938.
(56) Tsuzuki, Bull. Chem. Soc. Japan, 2, 78 (1927) [Chem. Zentr., I, 2651 (1927)].

TABLE I (continued)

Name of Compound	M. P.	Reference
Methyl-bis-[(2-dibenzofuroyl)-methyl]-amine hydrochloride	235-245(corr.)	(32)
Methyl 2-bromo-3-acetamino-6-dibenzofurancarboxylate	247-247.5	(8)pp.89,90
2-Methyldibenzofuro-[2,3-d]-imidazole	270	(13) p. 79
Methyl 2-methoxy-1-dibenzofuran-carboxylate	99.5-100	(55)
Methyl 2-methoxy-3-dibenzofuran-carboxylate	122.5	(55)
2-Methyl-5-methoxydibenzofuro-[1,2-d]-imidazole	222-222.5	(13) p. 82
2-Methylpyrido-[2,3-c]-dibenzofuran	185-186	(10) p. 85 (23)
N-Methyl-1,2,3,4-tetrahydrobenzofuro-[2,3-f]-quinoline	72-73(corr.)	(35)
N-Methyl-1,2,3,4-tetrahydrobenzofuro-[3,2-g]-quinoline	56-57(corr.)	(35)
1-Methyl-1,2,3,4-tetrahydropyrido-[2,3-c]-dibenzofuran hydrochloride	227-229(dec.)	(10) p. 84
3-Monoacetaminodibenzofuran	177-178	(22) (10) p. 68
Monobromo-3-aminodibenzofuran	133	(36)
Monobromo-3-diethylaminoethyl-aminodibenzofuran	66	(36)
Monobromo-1-hydroxydibenzofuran	178	(9) p. 53

TABLE I (continued)

Name of Compound	M. P.	Reference
1-Nitro-4-acetaminodibenzofuran	216	(24)
1-Nitro-4-aminodibenzofuran	219-220	(24)
1-Nitro-4-ethoxydibenzofuran	135-135.5	(18)
1-Nitro-4-methoxydibenzofuran	155	(18)
2-Nitro-3-acetaminodibenzofuran	196	(20) (22) (10) p. 69
2-Nitro-3-aminodibenzofuran	222	(22) (10) p. 70
2-Nitro-4-methoxydibenzofuran	185-186	(15) p. 84
3-Nitro-4-acetaminodibenzofuran	238	(24)
3-Nitro-4-aminodibenzofuran	185-186	(24)
3-Nitro-4-hydroxydibenzofuran	193	(18)
3-Nitro-4-methoxydibenzofuran	129.5	(18)
1-Oxo-2-dimethylaminomethyl-1,2,3,4-tetrahydro-β(or γ)-brazan hydrochloride	185-186	(15) p. 96
1,3,4,7,8-Pentamethoxydibenzofuran	109-110	(26)
3-Phenylaminodibenzofuran	132	(22)
Picrate of 4,6-diaminodibenzofuran	213 (dec.)	(17)
Picrate of 4,6-dimethoxydibenzofuran	161-162	(17)
Picrate of 4-hydroxydibenzofuran	122	(11)

TABLE I (continued)

Name of Compound	M. P.	Reference
Picrate of 4-methoxydibenzofuran	98-99	(11)
Picrate of 1,2,3,4-tetrahydro-7-aminodibenzofuran	187-188	(10) p.102
3-Pimelyldiaminodibenzofuran	264-265	(38)
2-ω-Piperidinoacetyldibenzofuran hydrochloride	270-271	(10) p. 91 (23)
2-(2-Piperidino-1-hydroxy)-ethyl-dibenzofuran benzoic acid ester	119 (corr.)	(32)
2-(2-Piperidino-1-hydroxy)-ethyl-dibenzofuran hydrochloride	250-251(corr.)	(32)
Piperidinomethyl-2-dibenzofuryl-carbinol	103-104	(23) (10) p. 91
2-(2-Piperidino-1-oxo)-ethyl-dibenzofuran hydrochloride	255-265(corr.) 270-271	(32) (23)
3-Piperidinodibenzofuran	111	(10) p. 81 (23)
3-(N-Piperidylethylamino)-dibenzofuran	87	(36)
3-(γ-N-Piperidyl-β-hydroxy-propylamino)-dibenzofuran	159	(36)
4-β-Piperidinoethoxydibenzofuran	210.5-212	(23)
1-Propenyl-2-hydroxydibenzofuran	94-95	(9) p. 33
3-n-Propylaminodibenzofuran hydrochloride	190	(23) (10) p. 78
Pyrido-[2,3-b]-and-[3,2-a]-dibenzofurans	185-186 160.5-161.5	(23) (10) p. 87

TABLE I (continued)

Name of Compound	M. P.	Reference
Pyrido-[2,3-c]-dibenzofuran	105.5-106	(10) p. 83 (23) (35)
Pyrido-[3,2-b]-dibenzofuran	167.5-168.5	(10) p. 82 (23) (35)
Quinoxaline of 2,3-diamino-dibenzofuran from benzil	179 184-185	(22) (6) p. 40 (10) p. 75 (20)
Quinoxaline of 2,3-diaminodibenzofuran from phenanthraquinone	297	(22) (6) p. 40 (10) p. 76 (20)
Quinoxaline of 3,4-diaminodibenzofuran from phenanthraquinone	277-278	(24)
2,3,7,8-Tetraacetoxydibenzofuran	262	(26)
3,4,6,7-Tetraacetoxydibenzofuran	247-251	(57)
3,4,6,7-Tetraacetoxydibenzofuran-1, 9-dicarboxylic acid	324-327	(57)
1,4,8,9-Tetraacetoxy-3,7-dimethoxy-dibenzofuran	255-256	(45)
3,4,6,7-Tetrabenzoyloxydibenzofuran-1 9-dicarboxylic acid	279-281(dec.)	(57)
1,2,3,4-Tetrahydro-7-acetamino-dibenzofuran	146	(10) p.102

(57) Nierenstein, Ann., 386, 318 (1912).

TABLE I (continued)

Name of Compound	M. P.	Reference
1,2,3,4-Tetrahydro-8-[γ-acetamino-n-propyl]-dibenzofuran hydrochloride	118	(21)
1,2,3,4-Tetrahydro-6-aminodibenzofuran hydrochloride	227-228	(17)
1,2,3,4-Tetrahydro-7-aminodibenzofuran	55-56	(10) p.101
1,2,3,4-Tetrahydro-8-[γ-amino-n-propyl]-dibenzofuran hydrochloride	253-254	(21)
1,2,3,4-Tetrahydrobenzofuro-[2,3-f]-quinoline	80-81(corr.)	(35)
1,2,3,4-Tetrahydrodibenzofuro-[3,2-g]-quinoline	111-112(corr.)	(35)
1,2,3,4-Tetrahydro-7-[2-(diethyl-amino)-1-oxo-ethyl]-dibenzo-furan hydrochloride	202-210(corr.)	(58)
1,2,3,4-Tetrahydro-7-[2-(dimethyl-amino)-1-hydroxy-ethyl]-dibenzofuran hydrochloride	220-222(corr.)	(58)
1,2,3,4-Tetrahydro-7-[2-(dimethyl-amino)-1-oxo-ethyl]-dibenz-furan hydrochloride	244-247(corr.)	(58)
1,2,3,4-Tetrahydro-4-methoxy-dibenzofuran	39-39.5	(12)

(58) Mosettig and Robinson, J. Am. Chem. Soc., 58, 688 (1936).

TABLE I (continued)

Name of Compound	M. P.	Reference
1,2,3,4-Tetrahydro-6-methoxy-dibenzofuran	39.5	(59) (60)
1,2,3,4-Tetrahydro-7-[2-(piperidino)-1-hydroxy-ethyl]-dibenzofuran hydrochloride	230-232(corr.)	(58)
1,2,3,4-Tetrahydro-7-[2-(piperidino)-1-oxo-ethyl]-dibenzofuran hydrochloride	235-239(corr.)	(58)
1,2,3,4-Tetrahydropyrido-[2,3-c]-dibenzofuran hydrochloride	247-248	(10) p. 84 (25) (35)
Tetrahydropyrido-[5,4-c]-dibenzofuran hydrochloride	259	(10) p. 99
1,2,3,4-Tetrahydro-7-[2-(1,2,3,4-tetrahydroisoquinolino)-1-hydroxy-ethyl]-dibenzofuran hydrochloride	197-200	(58)
1,2,3,4-Tetrahydro-7-[2-(1,2,3,4-tetrahydroisoquinolino)-1-oxo-ethyl]-dibenzofuran hydrochloride	230-264(corr.)	(58)
2,3,7,8-Tetrahydroxydibenzofuran	285 (dec.)	(61)
2,4,6,8-Tetrahydroxydibenzofuran	dec.above 300°	(62)

(59) Ebel, Helv. Chim. Acta, 12, 3 (1929).
(60) Gilman, Smith and Cheney, J. Am. Chem. Soc., 57, 2095 (1935).
(61) Schüler, Arch. Pharm., 245, 275 (1907).
(62) Selch, Monatsh., 14, 3 (1893).

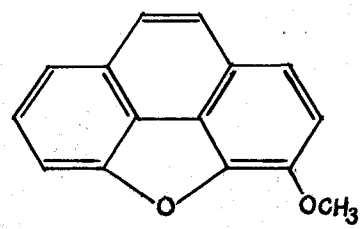
TABLE I (continued)

Name of Compound	M. P.	Reference
3,4,6,7-Tetrahydroxydibenzofuran	334-338(dec.)	(57)
3,4,6,7-Tetrahydroxydibenzofuran-1, 9-dicarboxylic acid (Purpurotannin	- - -	(57)
3,4,6,7-Tetramethoxydibenzofuran-1, 9-dicarboxylic acid	242-244(dec.)	(57)
1,4,8-Triacetoxy-3,7-dimethoxydibenzofuran	232	(26)
1,3,9-Tribenzeneazo-4,6-dimethoxydibenzofuran	191-193	(17)
1,4,8-Trihydroxy-3,7-dimethoxydibenzofuran	210(dec.)	(26)
1,4,8-Tri-p-nitrobenzoyloxy-3,7-dimethoxydibenzofuran	300	(8)

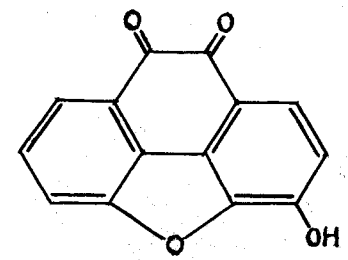
(63) Nietzki, Ann., 215, 163 (1882).
(64) German patent 48,709 [Frdl., 2, 410].
(65) German patent 44,784 [Frdl., 2, 407].
(66) German patent 50,140 [Frdl., 2, 412].

An inspection of Table I reveals that a surprisingly large number of compounds derived from the more readily accessible 2-amino-, 3-amino-, and 2-hydroxydibenzofurans have been described. Conversely, only a few amino and hydroxy derivatives wherein substitution involves the 1-, 4-, 6-, or 9-positions have been synthesized. Comparatively recent orientation and metalation studies have afforded a route to these hitherto unavailable, critically substituted dibenzofuran compounds of extraordinary pharmacological significance. A number of fascinating synthetic ideas present themselves.

As long ago as 1897, Vongerichten (67) clarified the nature of the indifferent oxygen atom in the morphine molecule through his researches on methylmorphenol (VI) (68), a substance which is formed in the final step of the exhaustive methylation of morphine (or codeine). Oxidation of acetylmorphenol followed by hydrolysis



VI. Methylmorphenol



VII. Morphenolquinone

(67) Vongerichten, Ber., 30, 2459 (1897); 31, 3198 (1898); 33, 352 (1900).

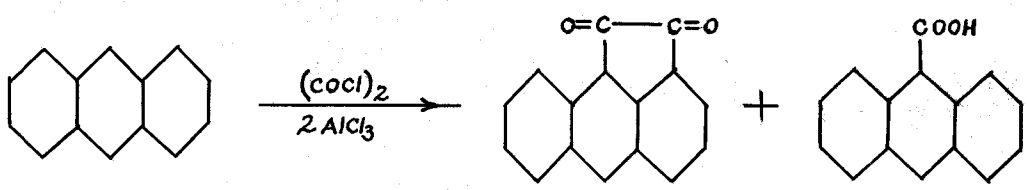
(68) Gilman, "Organic Chemistry", John Wiley and Sons Inc., New York, 1938, p. 1077.

resulted in the formation of the orange-red morphenolquinone (VII), which is also a 4,5-phenanthrylene oxide derivative.

So far, these degradation products have resisted all synthetic approach. Nevertheless, the likelihood of linking together the 1- and 9-positions of dibenzofuran by means of a two-carbon bridge for the synthesis of 4,5-phenanthrylene oxides finds the support of analogy in the literature.

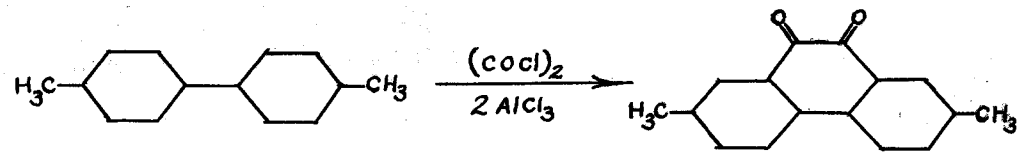
Polynuclear compounds have been prepared through the agency of the versatile Friedel-Crafts reaction wherein the comparable cyclization involved the linkage of a two-carbon chain.

Liebermann, in 1911, secured aceanthrenequinone (69) in excellent yield by reacting anthracene with oxalyl chloride in the presence of aluminum chloride. Some anthranoic acid was also formed in the reaction. Later he prepared 2,7-dimethylphenanthrenequinone (70) from 4,4'-dimethylbiphenyl and oxalyl chloride

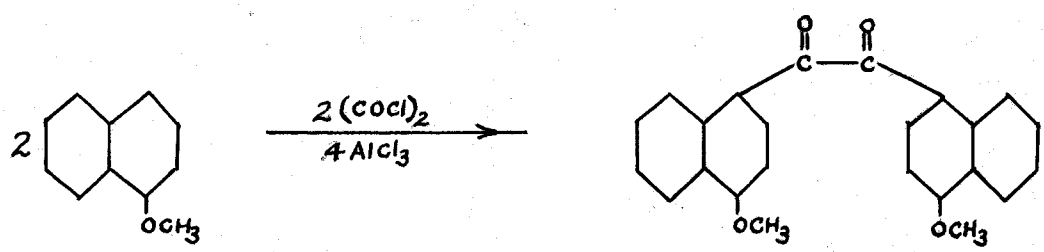


(69) Liebermann and Zsuffa, Ber., 44, 204, 856 (1911).
(70) Liebermann, Ber., 44, 1453 (1911); 45, 1186 (1912); 46, 198 (1913).

under similar conditions. The yield of o-quinone was 45-50%, diphenic acid being formed simultaneously in 25-50% quantity.



On the other hand, instead of the expected acenaphthenequinone derivative, Staudinger and co-workers isolated the unreactive bi-(1-methoxy-4-naphthoyl) in 60% yield when 1-methoxynaphthalene, oxalyl chloride and aluminum chloride were combined. (71)



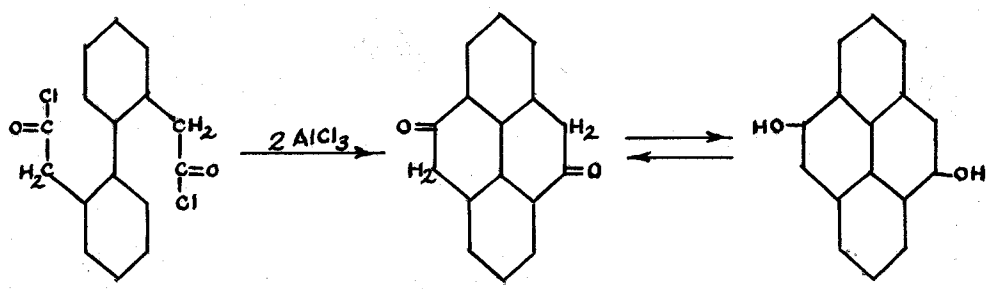
Not a trace of o-quinone could be isolated from the reaction mixture.

Lesser and Gad (72) obtained 3-4 g. of 2,7-dimethoxy-acenaphthenequinone from 10 g. of 2,7-dimethoxynaphthalene by

(71) Staudinger, Schlenker, and Goldstein, Helv. Chim. Acta, 4, 334 (1921).
(72) Lesser and Gad, Ber., 60, 242 (1927).

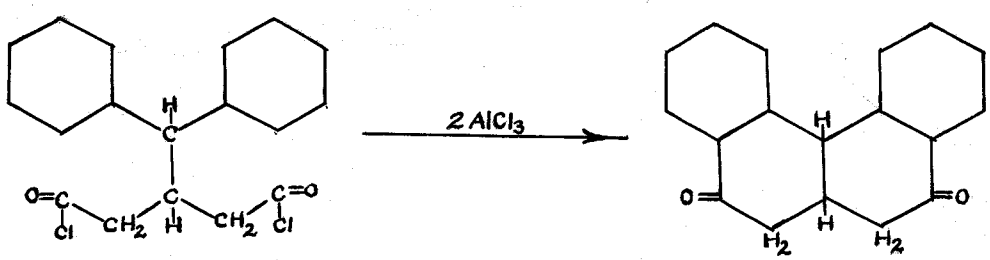
employing oxalyl chloride in the Friedel-Crafts reaction. Quite unexpectedly, the preponderant product proved to be 7-methoxy-β-naphthofuran-1,2-dione, resulting through cleavage of one of the methoxyl groups.

Weitzenböck's synthesis of pyrene (73) is a classical example of intramolecular condensation through the Friedel-Crafts reaction. When the acid chloride of 2,2'-biphenylenediacetic acid was treated with aluminum chloride at 0° for thirty minutes (nitrobenzene as solvent), an 85% yield of 1,6-dihydroxypyrene was isolated. Acenaphthenone was obtained in a similar manner from α-naphthylacetic acid (74). The yield was not mentioned in the patent.



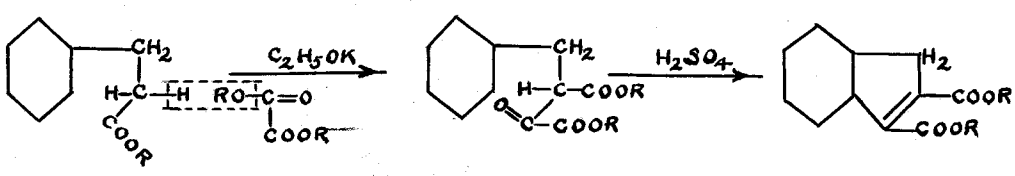
(73) Weitzenböck, Monatsh., 34, 193 (1913).
(74) German patent 230,237 [Frdl. 10, 199 (1910)].

A very recent synthesis of especial interest was conducted by Newman and Joshel (75). β-Benzohydrylglutaric acid chloride was intramolecularly condensed with aluminum chloride to produce 2,9-diketo-1,2,9,10,11,12-hexahydro-3,4-benzphenanthrene, an intermediate on a new synthetic route to 3,4-benzphenanthrene. The yield was 51.7% of the theoretical.



The Bougault reaction (76) has been successfully used for the synthesis of fused ring systems where applications of direct cyclization methods have failed. In 1915, Bougault discovered that the condensation product from β-phenylpropionic ester and oxalic ester is converted by concentrated sulfuric acid into the diester of indene-1,2-dicarboxylic acid. Von Auwers and

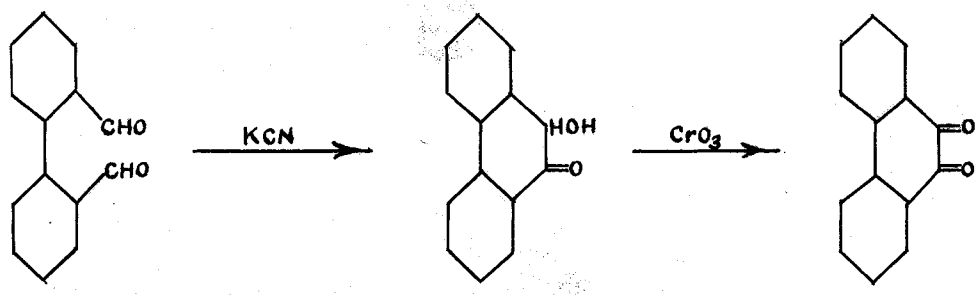
(75) Newman and Joshel, J. Am. Chem. Soc., 60, 485 (1938).
(76) Bougault, Compt. rend., 159, 745 (1915).



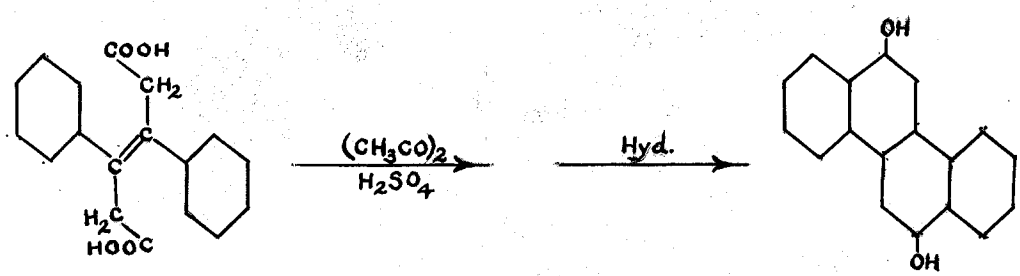
Möller (77), in 1925, applied the Bougault cyclization reaction to the next higher homolog to secure the anhydride of 3,4 dihydronaphthalene-1,2-dicarboxylic acid. Ten years later, Fieser and Hershberg (78) demonstrated that this cyclization was applicable to the γ-arylbutyric acids for the synthesis of polynuclear hydrocarbons, e.g., 3,4-dihydrophenanthrene-1,2-dicarboxylic acid anhydride. These yields are almost quantitative. It is reasonable to expect the Bougault reaction to be equally applicable to the cyclization of an arylacetic acid, provided that a six-membered ring can be formed.

Weitzenböck (73) transformed 2,2'-dialdehydobiphenyl into a phenanthrene derivative by means of the benzoin condensation. Subsequent oxidation produced a 50% yield of phenanthrenequinone, definitely establishing the formation of the two-carbon bridge.

(77) von Auwers and Möller, J. prakt. Chem., 109, 124 (1925).
(78) Fieser and Hershberg, J. Am. Chem. Soc., 57, 1851 (1935).



An excellent example of cyclization by direct water elimination is Beschke's synthesis of 2,8-dihydroxychrysene (79) from dihydrodiphenylmuconic acid. The condensation was

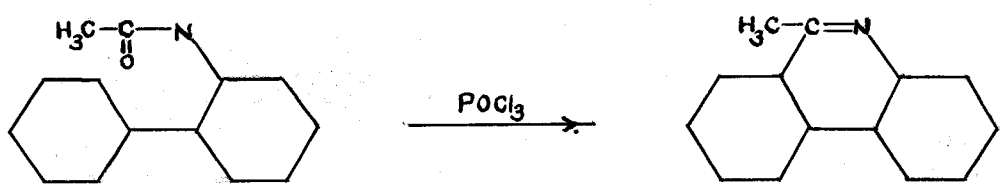


conducted by adding dropwise 5 ml. of concentrated sulfuric acid into an ice-cold solution of the muconic acid derivative in 40 ml. of acetic anhydride. 2,8-Diacetoxychrysene was obtained promptly in 86% yield. A smooth hydrolysis furnished the desired 2,8-dihydroxychrysene.

Various modifications of the Bischler-Napieralski reaction (80) have found considerable application in the synthesis of

(79) Beschke, Ann., 384, 151 (1911).
(80) Bischler and Napieralski, Ber., 26, 1903 (1893).

isoquinoline alkaloids (81). Phenanthridine derivatives, which contain not only an isoquinoline ring but also the quinoline nucleus, have been prepared by the same reaction. Morgan and Walls (82) observed that 9-methylphenanthridine, and also higher homologs, could be prepared in 75-80% yields from o-acylaminobiphenyls by utilizing phosphorus oxychloride as the condensing agent.



In 1909, Pictet and Gams synthesized papaverine (83), one of the opium alkaloids, by application of the Bischler-Napieralski reaction. Decker and co-workers (84), in 1913, published improved general conditions for the preparation of isoquinolines by this reaction. Since that time, a variety of complex alkaloids have been prepared by the judicious selection of solvents and condensing agents. The temperature and time variables also have a profound effect on the success of the reaction. In some

(81) Hollins, "Synthesis of Nitrogen Ring Compounds", Ernest Benn Limited, London, 1924, p. 510.
(82) Morgan and Walls, J. Chem. Soc., 1931, 2447; 1932, 2225.
(83) Pictet and Gams, Ber., 42, 2943 (1909).
(84) Decker and co-workers, Ann., 395, 299 (1913).

cases, phosphorus pentachloride at room temperature has proved successful when phosphorus pentoxide and phosphorus oxychloride have failed to afford any basic material. In 1928, for example, Gulland and Haworth (85) synthesized 5,6-dimethoxyaporphine in 90% yield by reacting a chloroform solution of the corresponding amide with phosphorus pentachloride at room temperature for twenty-four hours. Schlittler's comparatively recent synthesis of pukateine methyl ether (86) is a classical example of the advantageous use of phosphorus pentachloride as a condensing agent in the Bischler-Napieralski reaction.

Generalizations should be of distinct value in estimating the relative ease with which a particular cyclization can be expected to take place. An attempt has been made to glean pertinent observations from the literature.

Fieser and Bradsher (87) discovered that cyclization to form a six-membered ring at the 2-position of biphenyl was prevented by a meta methoxyl group situated at the 4-position. Researches on the cyclization of substituted benzoylbenzoic acids to produce the corresponding anthraquinones by Adams and co-workers (88, 89, 90) definitely established that ortho- and

(85) Gulland and Howarth, J. Chem. Soc., 1928, 581, 1132.
(86) Schlittler, Helv. Chim. Acta, 15, 381 (1932).
(87) Fieser and Bradsher, J. Am. Chem. Soc., 58, 1738 (1936).
(88) Graves and Adams, ibid., 45, 2439 (1923).
(89) Gardner and Adams, ibid., 45, 2455 (1923).
(90) Jacobson and Adams, ibid., 46,1512 (1924).

para-directing substituents attached meta to the position of condensation hindered the closure. Conversely, ortho- and para-directing groups situated in the ortho and para positions to that at which condensation was to take place materially facilitated the cyclization.

In the synthesis of substituted phenanthridines by ring closure, Morgan and Walls (82) noted that the presence of the strongly negative nitro group seriously inhibited the Bischler-Napieralski reaction provided that group were attached to the ring substituted in the cyclization. Following their attempts to synthesize isothebaine (91), Callow, Gulland, and Howarth concluded that ... "facile closure of the isoquinoline ring is dependent on the presence of a strongly p-directive group in the p-position to that at which condensation is to take place". They also found that an o,p-directing group placed meta to the carbon atom at which condensation is to take place greatly inhibited the Bischler-Napieralski reaction.

Calloway (92) has pointed out that the ease of substitution in an aromatic nucleus by the Friedel-Crafts reaction is enhanced by the introduction of positive substituents, such as the dimethylamino and methoxyl groups.

(91) Callow, Gulland, and Howarth, J. Chem. Soc., 1929, 1444.
(92) Calloway, Chem. Rev., 16-17, 371 (1935).

E X P E R I M E N T A L

Preparation of 3-Hydrazinodibenzofuran

This synthesis is an adaptation of the method used by Emil Fischer (93) to prepare ∝-naphthylhydrazine.

Nine and two-tenths grams (0.05 mole) of 3-aminodibenzofuran was triturated with 10 ml. of concentrated hydrochloric acid. The paste was washed into a 400 ml. beaker with 80 ml. of dilute hydrochloric acid (sp. gr. 1.10). The solution was warmed on a hot plate to ensure conversion to the chloride, and then cooled to -10° in an ice-salt bath. To this solution, which was thoroughly stirred with mechanical power and kept well below 0°, was slowly added from a dropping funnel (end of funnel under surface of liquid) a cold solution of 4.2 g. of sodium nitrite in 25 ml. of water. The yellow diazonium salt crystallized out in the form of beautiful needles. Stirring was continued for one-half hour.

A solution of stannous chloride, prepared by dissolving 50.0 g. of the hydrate in 50 ml. of concentrated hydrochloric acid, was cooled below 0° and slowly added by dropping funnel (end under surface of liquid) to the rapidly stirred suspension of diazonium salt. It was found necessary, during the addition, to add 10 ml. of concentrated hydrochloric acid to thin down the

(93) Fischer, Ann., 252, 237 (1885).

the thick, pasty mass of hydrazine hydrochloride which formed. Inasmuch as tin salts did not tend to form when the reaction was carried out below 0°, an ice-salt bath was utilized during the addition, and to ensure complete reaction, efficient stirring was continued for five hours while the bath gradually came to room temperature. (The diazonium solution is customarily added to the stannous chloride solution; the converse was practiced in this case for the sake of convenience.)

The white 3-hydrazinodibenzofuran hydrochloride was filtered off and crystallized from a large volume of water. It melted with decomposition at 242-243°. The yield was 10.3 g. or 87.3%.

Anal. Calcd. for $C_{12}H_{11}ON_2Cl$: N, 11.94. Found: N, 11.98.

The free 3-hydrazinodibenzofuran was obtained by decomposing a hot solution of the hydrochloride with sodium acetate. The base readily dissolved in hot alcohol, crystallizing from this solvent in the form of small pale yellow needles, m. p. 174-175°, which turned to an orange color in contact with the atmosphere.

Anal. Calcd. for $C_{12}H_{10}ON_2$: N, 14.14. Found: N, 14.09.

Borsche and Bothe (38) reported a melting point of 225° for the hydrochloride, and a value of 152° for the free base.

Preparation of 1,2,3,4-Tetrahydro-6-aminodibenzofuran

Two and five-tenths grams (0.0136 mole) of 4-aminodibenzofuran was dissolved in 100 ml. of absolute alcohol contained in a three-necked flask equipped with stirrer and reflux condenser. A nitrogen atmosphere was used throughout the reduction. While the solution was vigorously stirred, the sodium (8.0 g.) was added in small pieces through the top of the condenser. After the addition, which required twenty-five minutes, the solution was gently boiled to dissolve the remaining sodium. A noticeable amount of ammonia was evolved during the reduction.

The hot reaction mixture was poured promptly into a liter round-bottomed flask containing ice and hydrochloric acid in sufficient quantity to render the resulting solution acid to litmus. After removal of the alcohol by steam distillation, the mixture was immersed in a freezing mixture, made alkaline with 10% sodium hydroxide, and extracted thrice with a total volume of 400 ml. of ether. This red solution was dried over anhydrous sodium sulfate, and, following filtration, gaseous hydrogen chloride was introduced. The solid was filtered off and repeatedly washed with sodium-dried ether to remove a red resinous impurity adhering to the shiny pink plates of the hydrochloride. The yield was 1.9 g. or 62%. The salt was dissolved in water, digested with Norite, and filtered. Gaseous hydrogen chloride precipitated small pink plates which commenced to darken at 214°, melting at 228° with

decomposition. Attempts to prepare the free base were unsuccessful, the product remaining as an oil at 0°. The low hydrogen values indicate that some unreduced amine may be present as an impurity.

Anal. Calcd. for $C_{12}H_{14}NOCl$: C, 64.4; H, 6.31. Found: C, 64.4 and 64.4; H, 6.06 and 5.99.

In an effort to determine which ring had been reduced, the observation was made that a dry ether solution of tetra-hydro-4-aminodibenzofuran would not form a carbonate, although carbon dioxide was bubbled into the solution for an hour. Inasmuch as analogous alicyclic amines readily form carbonates, the evidence indicated that reduction had taken place in the unsubstituted ring.

Since all aromatic amines undergo diazotization, the following coupling reaction was conducted, which definitely established the aromatic nature of the reduced amine.

Five milliliters of dilute (6 N) hydrochloric acid was added to a solution of 0.1 g. (0.00045 mole) of tetrahydro-4-aminodibenzofuran hydrochloride in 15 ml. of water. Diazotixation was effected by cautiously adding a 5% solution of sodium nitrite to the ice-cold, well stirred solution until cadmium iodide-starch paper immediately turned blue when moistened with the stirring rod. After the clear yellow diazonium solution had stood for thirty minutes, it was slowly

added to a cold solution of 0.1 g. of β-naphthol in 25 ml. of 10% sodium hydroxide. A brilliant carmine red dye, m. p. 199-201°, immediately precipitated in quantitative yield (0.15 g.). The structure of the reduced amine, therefore, is known with certainty to be 1,2,3,4-tetrahydro-6-aminodibenzofuran.

Preparation of 4-Hydroxydibenzofuran

Inasmuch as large quantities of 4-hydroxydibenzofuran were required for the synthesis of 4,6-disubstituted derivatives, it was desirable to improve the reported yields, which have inconsistently varied over the wide range of 15.6-40% (consult Table I for references). Six one-mole preparations have been made by the following modified procedure to realize an average yield of 46.3% of 4-hydroxydibenzofuran based on the dibenzofuran. Despite an attempt to carefully control conditions, these yields varied as follows: 47.6%, 52.5%, 40.0%, 48.3% and 45.5%.

Into a suspension of 25.0 g. or more (a large excess) of finely cut lithium (the size of a grain of wheat) in 500 ml. of sodium-dried ether contained in a three-necked flask equipped with an efficient stirrer, Hopkin's condenser and dropping funnel, was added dropwise a solution of 205 g. (1.5 mole) of n-butyl bromide (dried over calcium chloride) in 250 ml. of ether. The n-butyl bromide was introduced into the rapidly stirred

suspension, which was protected by nitrogen, at such a rate that gentle refluxing was maintained. Stirring at room temperature was continued for at least one hour after the addition was complete.

The resulting n-butyllithium solution was strained under nitrogen through glass wool into a solution of 168 g. of dibenzofuran (dried in vacuum over sulfuric acid) in 500 ml. of ether contained in a three-liter flask equipped as above. Refluxing with slow stirring was continued overnight (16-18 hrs.). Then, in accordance with the procedure of Ivanoff (94), one mole of n-butylmagnesium bromide in 450 ml. of ether was added to improve the yield of oxidation product (9). The reaction mixture was cooled below zero degrees in an ice-salt mixture (low-temp. thermometer used), and oxygen (bubbled through sulfuric acid and passed over soda lime) was swept over the surface of the well stirred solution at such a rate that the temperature was maintained below zero until a negative color test (95) was obtained.

The lithium salt was hydrolyzed in a four-liter beaker containing ice and hydrochloric acid. The aqueous portion was extracted once with ether and discarded. The ether layers were combined in a four-liter separatory funnel, crushed ice was added, and extraction with 2-5% alkali was continued until no turbidity

(94) Ivanoff, Bull. soc. chim., 39, 47 (1926).
(95) Gilman and Schulze, J. Am. Chem. Soc., 47, 2002 (1925).

developed in an acidified portion. Norite was added to the alkaline solution, and dissolved ether was removed by gradual heating on a hot plate. The hot liquid was filtered, acidified, and cooled under the tap with shaking. The almost white 4-hydroxydibenzofuran thus obtained, melting at 99-100°, was pure enough for most synthetic purposes. One crystallization from petroleum ether (b. p. 77-115) produced very pale pink needles melting at 101-102°.

From the ether layer, appreciable amounts of bi-(4-dibenzofuryl) have been isolated, and its structure has been definitely established through synthesis (cf. the following experiment).

The yield of n-butyllithium from n-butyl bromide has been determined experimentally (96) to vary between 59-68.8%, depending on the particle size, in favor of the finely divided metal. A large excess of finely cut lithium has been found to very favorably increase the yield of metalation product. The unreacted metal can be saved in ether and be used in subsequent metalations.

Preparation of Bi-(4-dibenzofuryl) from 4-Dibenzofurylmagnesium Bromide

This preparation, an adaptation of the coupling reaction discovered by Krizewsky and Turner (97) and later successfully

(96) Gilman, Zoellner and Selby, J. Am. Chem. Soc., 55, 1252 (1933).
(97) Krizewsky and Turner, J. Chem. Soc., 115, 559 (1919).

applied to ∝-naphthylmagnesium bromide by Sakallarios and Kyrimis (98), was conducted for the purpose of positively identifying the supposed bi-(4-dibenzofuryl) isolated in the preparation of 4-hydroxydibenzofuran (cf. previous synthesis).

4-Dibenzofurylmagnesium bromide was prepared in the customary manner from 0.3 g. (0.0123 mole) of magnesium ribbon and 2.96 g. (0.012 mole) of 4-bromodibenzofuran dissolved in 30 ml. of sodium-dried ether. The reaction was easily started by the addition of the product obtained by heating a few magnesium filings with a crystal of iodine. The reagent, which was protected by a nitrogen atmosphere, was stirred at room temperature for two hours, then refluxed for one hour.

To the ice-cold, stirred Grignard reagent, was added 1.65 g. (0.0122 mole) of anhydrous cupric chloride suspended in 15 ml. of ether. After refluxing for two hours, the solution was cooled, decomposed with ice, and treated with concentrated hydrochloric acid to redissolve the precipitated cuprous chloride. The ether layer was separated, and the aqueous phase was thrice extracted with a total volume of 250 ml. of ether. The combined ether solutions were washed with 10% sodium carbonate solution, followed by water, and finally dried over anhydrous sodium sulfate.

Evaporation of the filtered ether solution was continued until crystals began to form. On cooling and filtering, 0.75 g. of colorless needles was obtained, m. p. 187-188.5°. Pure

(98) Sakallarios and Kyrimis, Ber., 57, 522 (1924).

bi-(4-dibenzofuryl), m. p. 191°, crystallized from acetic acid. Since 0.95 g. of compound was recovered from the filtrate, the total yield was 1.70 g. or 85%.

Anal. Calcd. for $C_{24}H_{14}O_2$: C, 86.2; H, 4.22. Found: C, 86.1; H, 4.29.

A mixed melting point determination proved that bi-(4-dibenzofuryl) is formed in the metalation and oxidation of dibenzofuran.

Friedel-Crafts Reaction with 4-Methoxydibenzofuran and Oxalyl Chloride

Into a solution of 9.90 g. (0.05 mole) of 4-methoxydibenzofuran and 7.0 g. (10% excess) of oxalyl chloride in 75 ml. of nitrobenzene contained in a three-necked flask equipped with stirrer and condenser topped with a calcium chloride tube, was gradually added 14.7 g. (10% excess) of anhydrous aluminum chloride. Throughout the addition an ice bath cooled the reaction mixture, which was then allowed to slowly come to room temperature. After twenty-eight hours, the red-brown mixture was hydrolyzed with ice and hydrochloric acid, the nitrobenzene was removed with steam, and the amorphous solid boiled with 5% sodium hydroxide solution and filtered. The dried acidification product from the filtrate (0.7 g.), after crystallization from acetic acid, melted at 276-277°

and was shown to be 4-methoxy-1-dibenzofurancarboxylic acid by mixed melting point.

The dried amorphous, alkali-insoluble solid was extracted with 100 ml. of acetic acid. From the cold filtrate was obtained 1.9 g. (18%) of di-(4-methoxy-1-dibenzofuryl) ketone in the form of colorless needles, m.p. 234°.

Anal. Calcd. for $C_{27}H_{18}O_5$: C, 76.8; H, 4.29. Found: C, 76.1; H, 4.37.

The acetic-acid insoluble residue, which proved to be bi-(4-methoxy-1-dibenzofuroyl), crystallized from nitrobenzene in the form of pale yellow needles, m. p. 529°. The yield was 3.9 g. or 34.6%.

Anal. Calcd. for $C_{29}H_{22}O_7$: C,72.2; H, 4.62. Found: C, 72.3; H, 4.68.

Not a trace of the hoped-for o-quinone could be found.

Friedel-Crafts Reaction with 4-Methoxydibenzofuran and Chloroacetyl Chloride

Into a solution of 12.5 g. (0.063 mole) of 4-methoxydibenzofuran and 7.9 g. (0.07 mole) of chloroacetyl chloride in 60 ml. of dry, ice-cold nitrobenzene contained in a flask equipped with mechanical stirrer and condenser, was introduced 8.5 g. (0.0635 mole) of anhydrous aluminum chloride, the addition extending over a thirty-minute interval. The bath was allowed to slowly come to room

temperature, and the reaction mixture was stirred for twenty-four hours. In an attempt to obtain an intramolecular condensation to form a 4,5-phenanthrylene oxide derivative, another 8.5 g. (0.0635 mole) of aluminum chloride was added to the cooled reaction flask.

After another twenty-four hours had elapsed, the reaction mixture was hydrolyzed with ice and hydrochloric acid; the solvent was removed with steam. The brown solid which remained was crystallized from benzene. The light tan needles of 1-chloroacetyl-4-methoxydibenzofuran thus obtained melted at 163-164°. The yield was 6.3 g. or 53.2%. Recrystallization from alcohol produced colorless needles of the pure compound melting at 165-166°.

Anal. Calcd. for $C_{15}H_{11}O_3Cl$: Cl, 12.92. Found: Cl, 13.12 and 13.05.

Several attempts to force the alkyl chlorine atom to take part in the Friedel-Crafts reaction were unsuccessful.

Preparation of 1-Ethoxalyl-4-methoxydibenzofuran

Into an ice-cold, stirred solution of 9.9 g. (0.05 mole) of 4-methoxydibenzofuran and 7.5 g. (10% excess) of ethyl chloroglyoxalate in 60 ml. of dry nitrobenzene, was gradually added 8.0 g. (20% excess) of anhydrous aluminum chloride. The dark red solution was allowed to slowly come to room temperature, stirring being continued for twenty-four hours. Steam distillation to remove the solvent followed customary hydrolysis with ice and

hydrochloric acid. The resulting brown, sticky solid was filtered from the cooled solution, dried, and twice crystallized from alcohol to produce colorless needles of 1-ethoxalyl-4-methoxydibenzofuran melting sharply at 113°. The yield of pure compound was 6.4 g. (43%).

Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.4; H, 4.73. Found: C, 68.0; H, 4.82.

Hydrolysis of 1-Ethoxalyl-4-methoxydibenzofuran

One gram (0.0037 mole) of 1-ethoxalyl-4-methoxydibenzofuran was suspended in 45 ml. of 15% sodium hydroxide solution and refluxed in the sand bath for seven hours. The contents were rinsed into a beaker with water enough to make the total volume 200 ml.; the resulting solution was heated to boiling and filtered. On slow cooling a silvery salt crystallized out. The chilled solution was filtered, the salt was washed with ice water, and a hot solution of the salt was acidified with hydrochloric acid to yield 430 mg. of pure, pale yellow 4-methoxy-1-dibenzofuryl-∝-oxoacetic acid, m. p. 187°. Small needles from alcohol exhibited no change in melting point. Concentrated sulfuric acid colored the keto acid deep red. Unfortunately, two attempts to reduce the keto group by the modified Clemmensen method of Martin (99) were unsuccessful, the keto oxygen emerging

(99) Martin, J. Am. Chem. Soc., 58, 1438 (1936).

unscathed.

Anal. Calcd. for $C_{15}H_{10}O_5$: C, 66.64; H, 3.73. Found: C, 66.39; H, 3.75.

In order to establish conclusively that the ethoxalyl group had entered the 1-position, a solution of 0.2 g. of the keto acid, 5 ml. of 10% sodium hydroxide, and 25 ml. of water was brought to a boil. Ten milliliters of 5% potassium permanganate solution was then added in small portions over a period of fifteen minutes. Dilute sulfuric acid was introduced until a distinct acid reaction to litmus was observed. After boiling the solution for five minutes, it was made alkaline with sodium hydroxide, Norite was added, heating was continued for another five minutes, and, finally, the solution was filtered and acidified. The cooled solution yielded 120 mg. of white acid, m. p. 277-278°. A mixed melting point determination with authentic 4-methoxy-1-dibenzofurancarboxylic acid established the identity of the two acids.

Preparation of 4-Methoxy-1-dibenzofuryl-α-oxoacetic Acid Semicarbazone

One-half gram of the keto acid was dissolved in 5 ml. of alcohol. Water was added until the solution was faintly turbid, the turbidity being removed with a few drops of alcohol. Then 0.5 g. of semicarbazide hydrochloride was added along with 0.75 g. of sodium acetate. The mixture was vigorously shaken, placed

in a beaker of hot water, and allowed to stand at room temperature for several days. The 4-methoxy-1-dibenzofuryl-α-oxoacetic acid semicarbazone slowly precipitated in quantitative yield. The white product, which was filtered from the cold, acidified solution, was recrystallized from alcohol to melt at 211.5-212° with decomposition.

Anal. Calcd. for $C_{16}H_{13}O_5N_3$: N, 12.84. Found: N, 12.83.

Metalation of 4-Methoxydibenzofuran with Subsequent Oxidation of the Metalation Product

Into a two-liter three-necked flask, equipped with a Hopkin's condenser, mechanical stirrer and dropping funnel, containing a suspension of 21 g. (3 gram atoms) of finely cut lithium in 500 ml. of sodium-dried ether, was added dropwise a solution of 205 g. (1.5 mole) of n-butyl bromide (dried over calcium chloride) in 250 ml. of ether. The addition was so regulated as to secure gentle reflux, and vigorous stirring was continued for one hour after addition was complete. A nitrogen atmosphere was employed.

The n-butyllithium solution was strained under nitrogen through glass wool into a solution of 198 g. (1 mole) of 4-methoxydibenzofuran in 500 ml. of dry ether contained in a three-liter flask equipped as above. A red-brown color immediately developed. Refluxing with constant stirring was continued for

six hours. A mole of n-butylmagnesium bromide in 500 ml. of ether was then added, under a nitrogen atmosphere, to favorably influence the oxidation (94), and the rapidly stirred solution, cooled below zero in an ice-salt bath, was subjected to a current of dry oxygen. The gas was swept over the surface of the liquid at such a rate that the temperature did not rise above zero until after five hours had elapsed and the escape of oxygen indicated that the oxidation was nearly complete. However, a pronounced color test (95) was obtained. After four more hours at zero degrees another positive test was observed. Therefore, the gray mixture was allowed to slowly warm up to room temperature while a stream of oxygen was passed over the surface. In this manner, a negative test was finally secured.

The mixture was poured into a four-liter beaker containing ice and hydrochloric acid, more acid being added with stirring until an acid reaction to litmus was obtained. The resulting suspension was then filtered to remove the alkali- and ether-insoluble white solid, the aqueous layer was extracted twice with ether, and the ether layer was washed with water. In order to separate the two isomeric phenols formed in the reaction, advantage was taken of the extreme difference in the solubility of their sodium salts. Equal amounts of the total yellow ether layer were placed in two two-liter Erlenmeyers, and 350 ml. of 10% sodium hydroxide solution was added to each flask with shaking.

The precipitated sodium salt of 4-hydroxy-6-methoxydibenzofuran was filtered off by suction, dissolved in 3.5 liters of water, boiled with Norite, and filtered through a steam funnel. The filtrate was acidified while warm and shaken while cooling under the tap to avoid the formation of large lumps of the phenol. The dry crude product (m. p. 101-106), weighing 49.4 grams, was recrystallized from petroleum ether (b. p. 60-68°) to yield 42.5 g. of 4-hydroxy-6-methoxydibenzofuran (19.8%) melting at 108-109°. Another crystallization from the same solvent raised the melting point of the colorless needles to 111-112°, which remained constant on further recrystallization. An alcoholic solution of the phenol was colored green by the addition of ferric chloride solution. A mixed melting point with an authentic specimen (15) showed no depression.

Isolation of the isomeric 3-hydroxy-4-methoxydibenzofuran was accomplished by the following procedure:

The aqueous layer of the filtrate was separated from the ether layer, which was further extracted with 2-3% alkali until no turbidity developed in an acidified portion. The alkaline solution, which had a volume of two liters, was digested with Norite and freed of ether before filtration and acidification. The crude 3-hydroxy-4-methoxydibenzofuran (57.1 g.) crystallized from 50% alcohol in the form of silky needles, m. p. 108-109°. The yield was 42.6 g. or 19.9%. Subsequent recrystallizations

raised the melting point to 109-110°. An alcoholic solution of this isomer developed a red-brown color with ferric chloride. A hot solution of 3-hydroxy-4-methoxydibenzofuran possesses a pleasant cinnamon-like aroma. The structure of the compound was definitely established by replacement of the amino group by hydroxyl in the known 3-amino-4-methoxydibenzofuran (cf. following experiment).

The ether-insoluble compound crystallized from acetic acid in the form of colorless needles, m. p. 257-258°. This product, which was later shown to be bi-(6-methoxy-4-dibenzofuryl), weighed 6.5 g. (3.6% of the theoretical). It is probable that the other coupling product, bi-(4-methoxy-3-dibenzofuryl) can be isolated from the ether solution, which contains definitely impure starting material. Furthermore, it is possible that the unsymmetrical coupling product is also formed in small amounts.

Preparation of 3-Hydroxy-4-methoxydibenzofuran from 3-Amino-4-methoxydibenzofuran

This reaction was conducted to definitely establish the structure of the isomer of 4-hydroxy-6-methoxydibenzofuran which had been isolated in the metalation and oxidation of 4-methoxydibenzofuran (cf. previous experiment).

Three-tenths of a gram (0.00141 mole) of pulverized 3-amino-4-methoxydibenzofuran* was dissolved in 75 ml. of

*Kindly supplied by Mr. A. L. Jacoby.

concentrated sulfuric acid at 0°, and a solution of 0.1 g. (0.00145 mole) of sodium nitrite in 10 ml. of water was slowly added to this ice-cold solution with thorough stirring. The resulting red-brown diazonium solution was poured over ca. 400 g. of ice.

After standing in an ice bath for one hour, the diazonium solution was added dropwise to a boiling solution of 75 g. of copper sulfate in 300 ml. of water contained in a distilling flask fitted to a condenser. Distillation was continued until a small volume remained, whereupon about 20 mg. of white solid, m. p. 104-106°, was obtained by steam distillation. The compound was sublimed at 90-100° by applying diminished pressure (4 mm.) to yield pale yellow needles of 3-hydroxy-4-methoxydibenzofuran melting at 107-108°. The pure compound, m. p. 109-110°, was secured by crystallization from water. An alcoholic solution of this authentic 3-hydroxy-4-methoxydibenzofuran, characterized by a cinnamon-like aroma, was colored red-brown by 1% ferric chloride solution.

A mixed melting point definitely established the identity of this compound and the 109-110°-melting isomer discovered while preparing 4-hydroxy-6-methoxydibenzofuran.

Anal. Calcd. for $C_{13}H_{10}O_3$: Methoxyl, 14.5 Found: Methoxyl, 14.1.

Preparation of Bi-(6-methoxy-4-dibenzofuryl) from 6-Methoxy-4-dibenzofurylmagnesium Bromide

Analyses, a molecular weight determination, and solubility considerations indicated that the ether-insoluble product, m. p. 237-238°, isolated after the metalation product of 4-methoxydibenzofuran had been oxidized, was very probably bi-(6-methoxy-4-dibenzofuryl). The following synthesis, an adaptation of the work of other investigators (97) (98), positively established the identity of this coupling product.

Using the conventional set-up, a Grignard reagent was prepared, under a nitrogen atmosphere, from 0.050 g. (0.002 mole) of magnesium ribbon and a solution of 0.40 g. (0.00144 mole) of 4-bromo-6-methoxydibenzofuran in 50 ml. of sodium-dried ether. A few magnesium filings were heated with a crystal of iodine in a small test tube and introduced for the purpose of initiating the reaction. The stirred mixture was refluxed overnight.

To the solution of 6-methoxy-4-dibenzofurylmagnesium bromide, immersed in an ice bath, was added 0.5 g. (0.0037 mole) of anhydrous cupric chloride. After thirty minutes, the reaction mixture was refluxed for two hours in a boiling water bath, the product was hydrolyzed with water, and the precipitated cuprous salt was dissolved by the addition of hydrochloric acid. The gray solid was filtered off and dissolved in boiling acetic acid. Small colorless

needles, m. p. 237-238°, quickly formed in the filtered solution. Recrystallization failed to raise the melting point. The yield was 0.175 g. (61.5%).

Anal. Calcd. for $C_{26}H_{18}O_4$: C, 79.2; H, 4.60. Found: C, 79.5; H, 4.52.

Molecular weight determination (Rast): Calcd.: 394. Found: 381.

No depression in melting point was observed when this compound was mixed with the ether-insoluble compound discovered when the metalation product of 4-methoxydibenzofuran was oxidized.

It is remarkable that the methoxyl groups of bi-(6-methoxy-4-dibenzofuryl) are not attacked under the imposed conditions of a Zeisel determination. This is probably due to the extreme insolubility of the compound in that medium, since slow demethylation was accomplished with a boiling solution of 48% hydrobromic acid in glacial acetic acid.

Demethylation of Bi-(6-methoxy-4-dibenzofuryl)

A suspension of 2.0 g. (0.00501 mole) of bi-(6-methoxy-4-dibenzofuryl) in 20 ml. of constant-boiling hydrobromic acid (sp. gr. 1.49) and 50 ml. of acetic acid was refluxed in a sand bath for twenty-nine hours and then poured into 300 ml. of water. The solid obtained by filtration was boiled with 200 ml. of 5%

sodium hydroxide solution. The acidified filtrate produced 1.43 g. (77% yield) of bi-(6-hydroxy-4-dibenzofuryl), m. p. 285-286°. The small shiny plates which crystallized from dilute alcohol possessed the same melting point.

Anal. Calcd. for $C_{24}H_{14}O_4$: C, 78.67; H, 3.85. Found: C, 78.4; H, 4.16.

A Zerewitinoff analysis gave 2.05 active hydrogens.

Preparation of 4,6-Dihydroxydibenzofuran

To a solution of 8.56 g. (0.04 mole) of 4-hydroxy-6-methoxydibenzofuran in 50 ml. of acetic acid was added 20 ml. of constant-boiling hydrobromic acid (sp. gr. 1.49). The reactants were refluxed in a sand bath for twelve hours, poured into 300 ml. of water, and placed in the refrigerator overnight. The small colorless needles obtained by filtration melted at 198-200°. The yield was 7.33 g. or 91.6% of the theoretical. The compound crystallized in the form of needles from dilute methanol to melt at 200-202°. Recrystallization from water and also from dilute methanol failed to raise or sharpen the melting point. The original 4,6-dihydroxydibenzofuran, prepared in very poor yield by oxidation of 4,6-disodiodibenzofuran and also by cleaving 4-hydroxy-6-methoxydibenzofuran with hydriodic acid, was reported to melt at 190° (15).

This smooth demethylation is essentially the method utilized by Mosettig and Meitzner (100) to obtain morphenol from its methyl ether.

Methylation of 3-Hydroxy-4-methoxydibenzofuran

Forty-nine and two-tenths grams (0.59 mole) of dimethyl sulfate was added dropwise to the solution obtained by dissolving 69.9 g. (0.326 mole) of 3-hydroxy-4-methoxydibenzofuran in 144.0 g. (0.36 mole) of 10% sodium hydroxide solution. Following addition, stirring was continued for one hour at the temperature of the steam bath. A solution of 9.0 g. (0.2 mole) of sodium hydroxide was then added to decompose the excess dimethyl sulfate (reaction conducted in the hood). Heating was continued for forty-five minutes.

The cooled reaction mixture was extracted thrice with a total of 450 ml. of ether. After drying over calcium chloride, the ether was distilled and the remaining brown oil was dissolved in low-boiling petroleum ether (b. p. 28-38°). A yield of 60.5 g. (81%) of pure 3,4-dimethoxydibenzofuran was secured. The colorless needles melted at 60-61°.

Anal. Calcd. for $C_{14}H_{12}O_3$: Methoxyl, 27.2. Found: Methoxyl, 26.8.

(100) Mosettig and Meitzner, J. Am. Chem. Soc., 56, 2738 (1934).

Demethylation of 3-Hydroxy-4-methoxydibenzofuran

A solution of 8.56 g. (0.04 mole) of 3-hydroxy-4-methoxydibenzofuran, 50 ml. of acetic acid and 20 ml. of constant-boiling hydrobromic acid (sp. gr. 1.49) was refluxed in a sand bath for nine hours, poured into 400 ml. of water and allowed to remain in the refrigerator overnight. Slightly discolored plates were filtered off and dried in vacuum. The product weighed 7.05 g. (88% yield), and melted at 162-163°. Recrystallization from water just brought to the boiling point produced colorless needles of 3,4-dihydroxydibenzofuran, m. p. 164-164.5°.

Anal. Calcd. for $C_{12}H_8O_3$: C, 71.98; H, 4.03. Found: C, 71.56; H, 4.21.

Methylation of 4-Hydroxy-6-methoxydibenzofuran

The slight solubility of the alkali salts of this phenol required the application of a special procedure in order to secure complete methylation. The following adaptation of the method utilized by Stevens and Tucker (101) to prepare N-alkylcarbazoles was recommended by Mr. R. H. Kirby of this laboratory. Excellent results were realized. Owing to the toxic nature of dimethyl sulfate, the reaction was conducted in the hood.

(101) Stevens and Tucker, J. Chem. Soc., 123, 2140 (1923).

Into a 250 ml. three-necked flask, equipped with stirrer, Hopkin's condenser, and dropping funnel, was placed 24.5 g. (0.115 mole) of 4-hydroxy-6-methoxydibenzofuran and 43.5 g. (0.345 mole) of dimethyl sulfate. Thirty-five ml. of acetone was then added to serve as a solvent. A 60% potassium hydroxide solution, prepared by dissolving 58.0 g. (1.04 moles) of the alkali in 39 ml. of water, was added dropwise to the vigorously refluxing, stirred solution over a forty-five minute period. Stirring at reflux temperature was continued for one and one-half hours, whereupon the product was poured into 700 ml. of water. The shiny crystals, m. p. 124.5-126°, were filtered off in quantitative yield (26.1 g.). Protracted cooling of a solution of 4,6-dimethoxydibenzofuran in petroleum ether (b. p. 60-68°) produced pearly plates, m. p. 128-129°. Recrystallization from alcohol did not alter the melting point.

Anal. Calcd. for $C_{14}H_{12}O_3$: Methoxyl, 27.2. Found: Methoxyl, 26.4.

Preparation of the Picrate of 4,6-Dimethoxydibenzofuran

Into a boiling solution of 0.55 g. (0.0024 mole) of picric acid in 5 ml. of alcohol, was poured a boiling solution of 0.50 g. (0.0022 mole) of 4,6-dimethoxydibenzofuran in 7 ml. of alcohol. A yellow, crystalline precipitate formed immediately. Boiling was continued for one minute, after which the flask was allowed

to cool slowly. The beautiful deep yellow needles melted at 160-161°. Recrystallization from alcohol raised the melting point to 161-162°. The insolubility of this picrate in petroleum ether rendered it an efficient tool to recover 4,6-dimethoxydibenzofuran from mother liquor.

Anal. Calcd. for $C_{14}H_{12}O_3 \cdot C_6H_3O_7N_3$: N, 9.19. Found: N, 9.11.

The isomeric 3,4-dimethoxydibenzofuran did not form a picrate when similar conditions were imposed.

Friedel-Crafts Reaction with 4,6-Dimethoxydibenzofuran and Oxalyl Chloride

The same apparatus and procedure were used as described for the Friedel-Crafts reaction of 4-methoxydibenzofuran and oxalyl chloride. Into an ice-cold solution of 4.56 g. (0.02 mole) of 4,6-dimethoxydibenzofuran and 2.8 g. (10% excess over 0.02 mole) of oxalyl chloride in 50 ml. of nitrobenzene, was slowly added 6.42 g. (20% excess over .04 mole) of powdered, anhydrous aluminum chloride. Addition required one and three-fourths hours, after which the reaction mixture was allowed to come to room temperature, stirring being continued for twenty hours. Hydrolysis was effected with ice and hydrochloric acid, after which the nitrobenzene was removed with steam. The remaining gray solid was extracted with 200 ml. of 10% sodium

hydroxide solution to remove any acids. Acidification of the filtrate furnished 0.37 g. of an acid which was later positively identified as 4,6-dimethoxy-1-dibenzofurancarboxylic acid, m. p. 297-298°.

The gray solid residue was extracted (Soxhlet apparatus used) with 100 ml. of acetic acid to yield 0.5 g. (10.4%) of di-(4,6-dimethoxy-1-dibenzofuryl) ketone, m. p. 254-255°.

Anal. Calcd. for $C_{29}H_{22}O_7$: C, 72.17; H, 4.62. Found: C, 72.31 and 71.54; H, 4.93 and 4.68.

Two attempts to prepare the oxime were unsuccessful.

The pale yellow, extremely insoluble residue from the acetic-acid extraction crystallized from nitrobenzene in the form of very small needles, m. p. above 300°. Analysis showed the compound to be bi-(4,6-dimethoxy-1-dibenzofuroyl). The yield was 3.1 g. (60.7% of the theoretical).

Anal. Calcd. for $C_{30}H_{22}O_8$: C, 70.65; H, 4.35. Found: C, 70.94 and 70.63; H, 4.60 and 4.69.

Preparation of 4-Bromo-6-methoxydibenzofuran

Twenty-one grams (3.1 gram atoms) of finely cut lithium was suspended in 700 ml. of sodium-dried ether, and a solution of 205 g. (1.5 moles) of n-butyl bromide in 250 ml. of ether was added dropwise to the rapidly stirred suspension. Stirring was continued for one hour after addition was complete.

Under a nitrogen atmosphere, the n-butyllithium was strained through glass wool into a flask containing 193 g. (0.975 mole) of 4-methoxydibenzofuran dissolved in 500 ml. of ether. The gently stirred solution, which soon turned plum-red in color, was allowed to remain overnight at reflux temperature.

After eighteen hours had elapsed, the metalation product was cooled to -10° in an ice-salt bath, and bromine vapor was swept into the cold solution by means of dry nitrogen bubbling through bromine, contained in a sulfuric acid wash bottle, which was warmed by a micro burner. During the time of introduction, the temperature was not allowed to rise above 0°. After several hours a negative color test (95) was obtained from the red-brown solution. Excess bromine was destroyed by the cautious addition of a saturated solution of sodium bisulfite to the rapidly stirred, ice-cold mixture. The ether layer was extracted with sodium bisulfite solution, washed with 10% sodium carbonate solution, then washed twice with water, and finally dried over sodium sulfate.

The ether was removed, following filtration, and the dark red-brown oil was distilled at diminished pressure. The fraction of b. p. 176-184° (4 mm.), weighing 69.9 g., solidified. It melted over a range of 75-91°. Four crystallizations from petroleum ether (b. p. 77-115°) raised the melting point to 114°. Another recrystallization from this solvent and also from alcohol

failed to alter the melting point of this compound, later proved to be the desired 4-bromo-6-methoxydibenzofuran. The yield was 19.7 g. or 7.3% of the theoretical.

Anal. Calcd. for $C_{13}H_9O_2Br$: Br, 28.85. Found: Br, 28.98.

Amination of this compound produced an aminomethoxy dibenzofuran dissimilar to the known 3-amino-4-methoxydibenzofuran. Inasmuch as metalation of 4-methoxydibenzofuran involves the 3- and 6-positions only, the compound must be, therefore, 4-bromo-6-methoxydibenzofuran. Accidental loss of the remaining mixture during distillation prevented the isolation of the isomeric 3-bromo-4-methoxydibenzofuran.

Demethylation of 4-Bromo-6-methoxydibenzofuran

A suspension of 0.5 g. (0.0018 mole) of 4-bromo-6-methoxydibenzofuran in 5 ml. of constant-boiling hydriodic acid (sp. gr. 1.67) was refluxed for two hours and then poured in 70 ml. of water. The resulting suspension was extracted with ether and the ether layer, in turn, was extracted with 10% sodium hydroxide. The aqueous layer was boiled with Norite, filtered and acidified. The white crude solid, m. p. 126-129°, was purified by recrystallization from water. The pure colorless needles of 4-bromo-6-hydroxydibenzofuran, m. p. 138-139°, weighed 95 mg. (19% yield). An alcoholic solution of this phenol gave a green color with ferric chloride solution.

Anal. Calcd. for $C_{12}H_7O_2Br$: Br, 30.39. Found: 30.47.

Preparation of 4-Amino-6-methoxydibenzofuran

An intimate mixture of 5 g. (0.018 mole) of 4-bromo-6-methoxydibenzofuran and 6 g. of freshly prepared cuprous bromide was placed in a large test tube, covered with 150 ml. of concentrated ammonium hydroxide, and electrically heated in a steel bomb at 100° for ten hours. The temperature was then raised to 215° and held constant for eight hours.

The cooled bomb was opened, the solid was pulverized in a mortar, and the contents were extracted twice with a total volume of 300 ml. of ether. The ether solution was dried over sodium sulfate, filtered, and subjected to a current of dry gaseous hydrogen chloride. The precipitated pale pink amine hydrochloride, m. p. 234-235°, weighed 1.95 g., representing a yield of 50.8%. The salt was dissolved in hot water, and, following digestion with Norite, hydrogen chloride was introduced into the filtrate to form beautiful, hair-like needles, m. p. 235-236° with slight discoloration.

Free 4-amino-6-methoxydibenzofuran, m. p. 109°, was obtained in the form of snow-white needles by adding ammonium hydroxide to a hot solution of the hydrochloride.

Anal. Calcd. for $C_{13}H_{11}O_2N$: N, 6.57. Found: N, 6.53.

Demethylation of 4-Amino-6-methoxydibenzofuran

A solution of 2.35 g. (0.0094 mole) of 4-amino-6-methoxydibenzofuran, 25 ml. of constant-boiling hydrobromic acid (sp. gr. 1.49), and 25 ml. of acetic acid was refluxed in a sand bath for nine hours. On slow cooling, 2.4 g. (81%) of 4-amino-6-hydroxydibenzofuran hydrobromide, m. p. 296° with decomposition, crystallized out. The hydrobromide was dissolved in 60 ml. of hot water, digested with Norite, filtered, and precipitated as the hydrochloride by the introduction of gaseous hydrogen chloride. The small white plates of 4-amino-6-hydroxydibenzofuran hydrochloride melted at 265-266° with decomposition. The yield was 1.85 g. or 78.7%.

The free base was obtained by dissolving the salt in hot water (several drops of hydrochloric acid were added to prevent hydrolysis), precipitating the aminophenol with saturated potassium sulfite solution, dissolving the precipitate by the addition of ammonium hydroxide, and, finally, precipitating the free base by cautiously adding 30% acetic acid solution until all trace of the odor of ammonia had vanished. The alkali-soluble, colorless needles of 4-amino-6-hydroxydibenzofuran thus obtained melted at 191.5-192.5°. The compound was not discolored by atmospheric oxygen.

Anal. Calcd. for $C_{12}H_9O_2N$: N, 7.03. Found: N, 7.15.

Bromination of 3,4-Dimethoxydibenzofuran

To a solution of 1.5 g. (0.0066 mole) of 3,4-dimethoxydibenzofuran in 15 ml. of acetic acid was slowly introduced (with shaking) 13.4 ml. of a 0.5 molar solution of bromine in acetic acid. Decolorization progressed rapidly. After standing overnight the solution was diluted with water, and the white solid was filtered off. Crystallization from alcohol gave 1.79 g. (88.5% yield) of 1-bromo-3,4-dimethoxydibenzofuran, m. p. 107-108°. Recrystallization from the same solvent furnished hair-like needles, m. p. 108°.

Anal. Calcd. for $C_{14}H_{11}O_3Br$: Br, 26.03. Found: Br, 26.11.

The structural proof is delineated in the following experiment.

Bromination of 3-Hydroxy-4-methoxydibenzofuran

To a stirred solution of 4.28 g. (0.02 mole) of 3-hydroxy-4-methoxydibenzofuran in 50 ml. of acetic acid was slowly introduced 40 ml. of a 0.5 molar solution of bromine in acetic acid. The decolorization was almost instantaneous. Dilution of the reaction mixture, followed by filtration, furnished 5.65 g. of substance which melted at 130-149°, indicating that isomers were probably present. After one crystallization from 30% alcohol

and three recrystallizations from benzene, white fluffy needles of 1-bromo-3-hydroxy-4-methoxydibenzofuran, m. p. 161-162° were obtained. The yield was 3.1 g. or 54.6% of the theoretical. No attempt was made to isolate the more soluble isomer.

Anal. Calcd. for $C_{13}H_9O_3Br$: Br, 27.28. Found: Br, 27.32.

An intimate mixture of this compound and authentic 1-bromo-3-hydroxy-4-methoxydibenzofuran prepared from the known 1-bromo-3-amino-4-methoxydibenzofuran exhibited no melting point depression.

1-Bromo-3,4-dimethoxydibenzofuran, m. p. 108°, was prepared by methylating 0.5 g. of 1-bromo-3-hydroxy-4-methoxydibenzofuran at room temperature with 3 ml. of dimethyl sulfate and 5 ml. of 10% sodium hydroxide solution. The compound obtained by direct bromination of 3,4-dimethoxydibenzofuran was proved identical by a mixed melting point determination.

Conversion of 1-Bromo-3-amino-4-methoxydibenzofuran to 1-Bromo-3-hydroxy-4-methoxydibenzofuran

To an ice-cold solution of 0.22 g. (0.0052 mole) of sodium nitrite in 75 ml. of concentrated sulfuric acid was added 0.95 g. (0.00325 mole) of pulverized 1-bromo-3-amino-4-methoxydibenzofuran. The resulting diazonium sulfate solution was poured over ca. 450 g. of ice and allowed to stand

in the refrigerator for two hours. This solution was then added dropwise to a boiling solution of 75 g. of copper sulfate in 250 ml. of water contained in a distilling flask fitted with a condenser. The white solid which steam distilled was dissolved in 5% sodium hydroxide solution, treated with Norite, filtered, and acidified. The white needles of authentic 1-bromo-3-hydroxy-4-methoxydibenzofuran thus obtained, m. p. 161-162°, weighed 0.2 g. (21% yield). No depression in melting point was observed when this compound was mixed with the bromination product of 3-hydroxy-4-methoxydibenzofuran.

Preparation of 1-Bromo-4,6-dimethoxydibenzofuran

To a vigorously stirred solution of 22.8 g. (0.1 mole) of 4,6-dimethoxydibenzofuran in 600 ml. of acetic acid was added dropwise 100 ml. of a molar solution of bromine in acetic acid. Small white crystals appeared just before addition was complete. The reaction mixture was then stirred for two hours at room temperature, whereupon it was poured into one liter of water, and the solid filtered off. The crude 1-bromo-4,6-dimethoxydibenzofuran, m. p. 147-148.5°, was obtained in 95% yield. Crystallization from one and one-half liters of alcohol produced 22.4 g., a 73% yield, of pearly white plates melting sharply at 152°. Concentration of the mother liquor led to the

recovery of 3.7 g. (12%) of product melting at 144-147°.

Anal. Calcd. for $C_{14}H_{11}O_5Br$: Br, 26.01. Found: Br, 26.23.

Dibromination of 4,6-Dimethoxydibenzofuran

To a rapidly stirred solution of 3.0 g. (0.0132 mole) of 4,6-dimethoxydibenzofuran in 120 ml. of acetic acid was added 52.7 ml. of a 0.5 molar solution of bromine in acetic acid. Stirring was continued for thirty minutes after addition was complete. Next morning it was observed that white needles had deposited. The yellow solution was heated on the water bath for one and one-half hours and cooled. By filtration, 2.85 g. of silky needles of 1,9-dibromo-4,6-dimethoxydibenzofuran, m. p. 167-168°, was obtained. Recovery of 0.92 g. of pure compound from the acetic acid solution gave a total yield of 3.77 g. or 74%.

Anal. Calcd. for $C_{14}H_{10}O_3Br_2$: Br, 41.42. Found: Br, 41.60.

Dibromination of 4,6-Dihydroxydibenzofuran

To a solution of 2.0 g. (0.01 mole) of 4,6-dihydroxydibenzofuran in 20 ml. of acetic acid was slowly added (with constant shaking) 40 ml. of a 0.5 molar solution of bromine in acetic acid. Decolorization was instantaneous. A precipitate

slowly formed. After standing overnight, the reaction mixture was poured into 250 ml. of water, and crude 1,9-dibromo-4,6-dihydroxydibenzofuran, m. p. 237-239° with decomposition, was filtered off in quantitative yield. The pure compound, m. p. 239-241° with decomposition, was secured by crystallization from xylene.

Anal. Calcd. for $C_{12}H_6O_3Br_2$: Br, 44.66. Found: Br, 44.77.

Evidence for the assigned structure was obtained by the following methylation:

Into a solution of 1.0 g. (0.0028 mole) of dibromo-4,6-dihydroxydibenzofuran in 10 ml. of acetone contained in a three-necked flask, equipped with stirrer, condenser, and dropping funnel, was poured 4.77 g. (0.0378 mole) of dimethyl sulfate. A solution of 6.35 g. (0.113 mole) of potassium hydroxide in 5 ml. of water was then added dropwise to the refluxing, stirred solution. Stirring was continued for thirty minutes, and the reaction mixture was then diluted with water and filtered. The crude product (quantitative yield) was purified by crystallization from acetic acid. The long silky needles thus obtained, m. p. 167-168°, were identical (mixed melting point determination) with those secured by the direct dibromination of 4,6-dimethoxydibenzofuran.

Dibromination of 4-Hydroxy-6-methoxydibenzofuran

To a solution of 2.14 g. (0.01 mole) of 4-hydroxy-6-methoxydibenzofuran in 20 ml. of acetic acid was slowly added 40 ml. of a 0.5 molar solution of bromine in acetic acid. Decolorization was not rapid, considerable shaking being required to dispel the bromine color. Colorless needles slowly formed. After standing overnight at room temperature, the reaction mixture was cooled and filtered to obtain 2.17 g. of a pure dibromo compound, m. p. 177-178°, which is very probably 1,3-dibromo-4-hydroxy-6-methoxydibenzofuran (cf. following experiment).

Anal. Calcd. for $C_{13}H_8O_3Br_2$: Br, 42.98. Found: Br, 43.10.

Methylation of 1,3-dibromo-4-hydroxy-6-methoxydibenzofuran

To a refluxing solution of 0.5 g. (0.00135 mole) of 1,3-dibromo-4-hydroxy-6-methoxydibenzofuran and 4.77 g. (0.0378 mole) of dimethyl sulfate in 10 ml. of acetone was added dropwise with stirring a solution of 6.35 g. (0.113 mole) of potassium hydroxide in 5 ml. of water. Refluxing was continued for thirty minutes after addition was complete. The reaction mixture was diluted with 200 ml. of water and filtered to obtain a quantitative yield of methylated product. Long, colorless needles of 1,3-dibromo-4,6-dimethoxydibenzofuran,

m. p. 173.5-174°, crystallized from acetic acid. A depression in melting point was observed when this compound was intimately mixed with 1,9-dibromo-4,6-dimethoxydibenzofuran.

Anal. Calcd. for $C_{14}H_{10}O_3Br_2$: Br, 41.42. Found: Br, 41.68.

Preparation of 4,6-Diaminodibenzofuran

The method of Bucherer (102), which has been effectively utilized in recent years by Fieser and co-workers (103) furnished 4,6-diaminodibenzofuran in excellent yield.

In each of four Carius tubes, a mixture of 1.0 g. (0.005 mole) of 4,6-dihydroxydibenzofuran, 7.5 g. of sodium bisulfite dissolved in 15 ml. of water, and 15 ml. of concentrated ammonium hydroxide was sealed, the tubes were then heated at 185-195° in an electric furnace for twenty hours. The cooled mixtures were combined and extracted thrice with a total volume of 400 ml. of ether. The ether solution was washed thoroughly with 10% sodium hydroxide solution and then with water. The 4,6-diaminodibenzofuran hydrochloride, m. p. 297-298° with decomposition, was precipitated from the dried ether solution by the introduction of dry gaseous hydrogen chloride. The yield was 4.4 g. or 81% of the theoretical. The hydrochloride

(102) Bucherer, J. prakt. Chem., 69, 49 (1904).
(103) Fieser and co-workers, J. Am. Chem. Soc., 58, 2163 (1936); 59, 478 (1937).

was dissolved in about 25 ml. of hot water, digested with Norite, filtered and precipitated again with gaseous hydrogen chloride. Snow-white needles formed which melted at 298° with decomposition.

Anal. Calcd. for $C_{12}H_{12}ON_2Cl_2$: N, 10.33. Found:* N, 10.52.

The free 4,6-diaminodibenzofuran was liberated by the addition of ammonium hydroxide to a solution of the hydrochloride. The compound crystallized from methanol in the form of colorless prisms, m. p. 152°.

Preparation of the Picrate of 4,6-Diaminodibenzofuran

Into a boiling solution of 0.45 g. (0.00227 mole) of 4,6-diaminodibenzofuran in 2 ml. of alcohol was poured a boiling solution of 0.55 g. (0.0024 mole) of picric acid in 2 ml. of alcohol. The red-brown picrate crystallized immediately in the form of shiny plates. More alcohol (6 ml.) was added, the solution was boiled one minute, cooled and filtered to secure a product melting at 212° with decomposition. Recrystallization from alcohol produced shiny red-brown plates, m. p. 215° with pronounced decomposition.

Anal. Calcd. for $C_{12}H_{10}ON_2 \cdot C_6H_3O_7N_3$: N, 16.40. Found: N, 16.28.

* The author is grateful to Mr. T. H. Cook for this micro-Kjeldahl analysis.

Preparation of 4,6-diacetaminodibenzofuran

To a solution of 0.5 g. (0.00252 mole) of 4,6-diaminodibenzofuran in 20 ml. of warm benzene was added 1 ml. of acetic anhydride. The insoluble 4,6-diacetaminodibenzofuran precipitated immediately. After 80 ml. of additional benzene had been added, the suspension was boiled, cooled, and filtered. A quantitative yield of the crude product was obtained. Crystallization from acetic acid produced very small colorless needles, m. p. 297-298°.

Anal. Calcd. for $C_{16}H_{14}O_3N_2$: N, 9.93. Found: N, 9.92.

Preparation of 4,6-Diacetoxydibenzofuran

One gram (0.005 mole) of 4,6-dihydroxydibenzofuran was dissolved in 10 ml. of acetic anhydride by the application of heat, and one drop of concentrated sulfuric acid was introduced into the warm solution, which immediately turned reddish-brown. Considerable heat was evolved in the reaction. After thirty minutes had elapsed, the reaction mixture was poured into 110 ml. of water, and excess acetic anhydride was hydrolyzed by boiling the mixture. The cooled solution yielded 1.25 g. of crude product. Pure 4,6-diacetoxydibenzofuran, m. p. 177°, crystallized from methanol in the form of small, shiny plates. The yield of this pure product was 0.75 g. or 53% of the theoretical.

Anal. Calcd. for $C_{16}H_{12}O_5$: C, 67.5; H, 4.28. Found: C, 67.4; H, 4.31.

Preparation of 3,4-Diacetoxydibenzofuran

To a warm solution of 1.95 g. (0.00975 mole) of 3,4-dihydroxydibenzofuran in 10 ml. of acetic anhydride was added one drop of concentrated sulfuric acid. After the excess acetic anhydride had been hydrolyzed by boiling the reaction mixture with 100 ml. of water, the diacetoxy compound, in the form of an oil, was extracted with ether. Evaporation of the dried ether solution left 2.05 g. (74.1%) of crude 3,4-diacetoxydibenzofuran, m. p. 100-102°. Crystallization from methanol elevated the melting point to 104-105°.

Anal. Calcd. for $C_{16}H_{12}O_5$: C, 67.5; H, 4.28. Found: C, 67.6; H, 4.21.

Acetylation of 4,6-Dimethoxydibenzofuran

Into a flask equipped with stirrer and condenser topped with a calcium chloride tube was introduced a solution of 17.35 g. (0.0761 mole) of 4,6-dimethoxydibenzofuran and 5.97 g. (0.0761 mole) of acetyl chloride in 100 ml. of anhydrous nitrobenzene. After the stirred reaction mixture had been immersed in an ice bath for thirty minutes, 10.18 g. (0.0761 mole) of powered anhydrous aluminum chloride was introduced

in small portions over a period of one hour. After addition was complete, the contents of the flask were allowed to slowly come to room temperature, and stirring was continued for twenty hours.

Hydrolysis with ice and hydrochloric acid preceded removal of the nitrobenzene with steam. An attempt to dissolve all of the remaining red solid in one liter of 1:1 benzene-ether met with failure. Therefore, the pink solid was filtered off, washed thoroughly with 10% sodium carbonate solution followed by water, and finally dried. Crystallization from alcohol yielded 8.05 g. of very pale pink prisms, m. p. 178.5-179.5°. Recrystallization from alcohol or dilute acetone produced a colorless compound, but the melting point remained constant.

The red ether-benzene solution was washed with 10% sodium carbonate solution, digested with Norite, filtered, and the solvent steam distilled. The resulting light red solid was boiled with a liter of alcohol and filtered to remove a small quantity of amorphous red dye which melted above 300°. On cooling the solution, colored crystals separated which melted at 173-175°. Recrystallization from benzene furnished 4.3 g. of pink prisms of 1-acetyl-4,6-dimethoxydibenzofuran melting at 178-179°. The total yield of pure product, therefore, was 12.35 g. or 60% of the theoretical.

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.18 and 71.30; H, 4.93 and 5.08.

It was proved that the acetyl group had entered the 1-position by preparing the oxime, transforming the oxime to the acetamino derivative and, finally, hydrolyzing off the acetyl group to arrive at the established 1-amino-4,6-dimethoxydibenzofuran prepared by reduction of 1-benzeneazo-4,6-dimethoxydibenzofuran.

Acetylation of 3,4-Dimethoxydibenzofuran

The same set-up and general procedure were utilized as in the acetylation of the isomeric 4,6-dimethoxydibenzofuran (cf. previous experiment).

To an ice-cold solution of 15.68 g. (0.06 mole) of 3,4-dimethoxydibenzofuran and 4.65 ml. (10% excess over 0.06 mole) of acetyl chloride in 60 ml. of dry nitrobenzene was slowly introduced 9.6 g. (20% excess over 0.06 mole) of anhydrous, powdered aluminum chloride. After the reaction mixture had stirred at room temperature for twenty-four hours, hydrolysis was accomplished with ice and hydrochloric acid, and the nitrobenzene was removed with steam. The remaining black solid was filtered off, dissolved in 500 ml. of ether, and extracted with 300 ml. of 10% sodium carbonate solution. A yellow salt precipitated which was removed by filtration and later combined with the

sodium carbonate extract. From this alkaline solution, after Norite treatment, filtration and acidification, was obtained 2.79 g. of dry acidic material which crystallized from alcohol in the form of small colorless needles, m. p. 201-202°. This partially or completely demethylated phenol was not further investigated.

The ether layer was washed with water, dried over sodium sulfate, filtered, and the ether distilled. The remaining tan solid (11.2 g.) melted at 88-89°. Crystallization from alcohol produced 9.50 g. (55.5% yield) of almost colorless needles of 1-acetyl-3,4-dimethoxydibenzofuran, m. p. 90°. Recrystallization from alcohol, after treatment with Norite, yielded colorless needles, m. p. 90.5-91°.

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.11 and 70.54; H, 5.41 and 5.42.

It was ascertained that the acetyl group occupied the 1-position by preparing an amino-3,4-dimethoxydibenzofuran through hydrolysis of the acetamino derivative obtained by Beckmann rearrangement of the oxime. A mixed melting point determination with this amine and authentic 1-amino-3,4-dimethoxydibenzofuran, prepared by amination of the known 1-bromo-3,4-dimethoxydibenzofuran, showed no depression.

Preparation of the Oxime of 1-Acetyl-4,6-dimethoxydibenzofuran

The procedure described here is essentially that which Parker (13) employed to prepare the oxime of 1-acetyl-4-methoxydibenzofuran.

To a solution of 6.72 g. (0.0248 mole) of 1-acetyl-4,6-dimethoxydibenzofuran in 100 ml. of alcohol was added 2.4 g. (0.0345 mole) of hydroxylamine hydrochloride and 6.25 g. (0.111 mole) of potassium hydroxide dissolved in 15 ml. of water. The resulting mixture was refluxed on the hot plate for five hours, poured into 300 ml. of water, made acid with acetic acid and filtered. The quantitative yield (7.1 g.) of white solid thus obtained melted at 197-198.5°. Crystallization from alcohol (slow cooling) produced 6.22 g. (87.6% yield) of large pale pink plates of 1-acetyl-4,6-dimethoxydibenzofuran oxime, m. p. 201-202°. Subsequent recrystallization from the same solvent elevated the melting point to 203-204°.

Anal. Calcd. for $C_{16}H_{15}O_4N$: N, 4.91. Found: N, 5.02.

Preparation of the Oxime of 1-Acetyl-3,4-dimethoxydibenzofuran

Following the procedure of Parker (13), a mixture of 5.0 g. (0.0185 mole) of 1-acetyl-3,4-dimethoxydibenzofuran, 1.9 g. (0.0273 mole) of hydroxylamine hydrochloride, 75 ml. of alcohol, and 5.0 g. (0.089 mole) of potassium hydroxide in 15 ml. of water was refluxed on the hot plate for five hours. The reaction

mixture was poured into 200 ml. of water and acidified with acetic acid. Filtration furnished a quantitative yield of crude oxime, m. p. 152-154°. Recrystallization from alcohol gave colorless needles of pure 1-acetyl-3,4-dimethoxydibenzofuran oxime, m. p. 156-157°. The yield of pure compound was 4.42 g. or 84%.

Anal. Calcd. for $C_{16}H_{15}O_4N$: N, 4.91. Found: N, 5.11.

Beckmann Rearrangement of 1-Acetyl-4,6-dimethoxydibenzofuran Oxime

To a suspension of 3.5 g. (0.0123 mole) of 1-acetyl-4,6-dimethoxydibenzofuran oxime in 300 ml. of anhydrous benzene was added, in one portion, 3.5 g. (0.0168 mole) of pulverized phosphorus pentachloride. The reaction mixture was shaken for two minutes, during which time the phosphorus halide dissolved, and the clear solution turned pale green in color. This rearrangement was noticeably exothermic.

The hot, clear solution was poured on ice, made alkaline with 10% sodium carbonate solution and then just acid with acetic acid. The benzene was removed with steam, and a quantitative yield of the white crude product, m. p. 241-242.5°, was filtered off. Crystallization from alcohol raised the melting

point of the 1-acetamino-4,6-dimethoxydibenzofuran to 244°. The yield was 2.67 g. or 76.4%. Recrystallization from benzene produced white microcrystalline needles, m. p. 244-245°.

Anal. Calcd. for $C_{16}H_{15}O_4N$: N, 4.92. Found: N, 4.95.

This procedure, employed by Parker (13) for the rearrangement of 1-acetyl-4-methoxydibenzofuran oxime, is somewhat similar to that applied by Bachmann and Boatner (104) to phenanthrene chemistry.

Beckmann Rearrangement of 1-Acetyl-3,4-dimethoxydibenzofuran Oxime

To a solution of 3.5 g. (0.0123 mole) of 1-acetyl-3,4-dimethoxydibenzofuran oxime in 50 ml. of anhydrous benzene was added, in small portions, 3.5 g. (0.0168 mole) of pulverized phosphorus pentachloride. A vigorous reaction took place. After standing for five minutes, the red-brown solution was poured on ice, made alkaline with sodium carbonate solution, and then acetic acid was introduced until the mixture was definitely acid to litmus. Subsequent to the removal of the benzene by steam distillation, 3.3 g. (94%) of the crude 1-acetamino-3,4-dimethoxydibenzofuran, m. p. 191-192° was obtained. The slightly discolored product was

(104) Bachmann and Boatner, J. Am. Chem. Soc., 58, 857, 2097 (1936).

dissolved in 40 ml. of alcohol, and several drops of acetic anhydride were added to convert any free amine to the amide. Following digestion with Norite, the filtered solution was slowly cooled. White needles, m. p. 196-196.5°, were thus secured.

Anal. Calcd. for $C_{16}H_{15}O_4N$: N, 4.92. Found: N, 5.02.

Preparation of 1-Benzeneazo-4-hydroxy-6-methoxydibenzofuran

The remarkable insolubility of the potassium salt of 4-hydroxy-6-methoxydibenzofuran required a modification of the procedure employed by Mrs. VanEss (8) to couple 4-hydroxydibenzofuran.

The alkaline solution of the phenol prepared from 4.28 g. (0.02 mole) of 4-hydroxy-6-methoxydibenzofuran, 15 ml. of 15% potassium hydroxide solution, and 385 ml. of water, was placed in a one-liter three-necked flask equipped with stirrer, low-temperature thermometer and dropping funnel.

The diazonium salt solution was prepared by dissolving 2.58 g. (0.02 mole) of aniline hydrochloride in 15 ml. of water, cooling the solution in an ice bath, adding 15-25 g. of cracked ice, introducing 3.4 ml. of concentrated hydrochloric acid, and, finally, adding cautiously a solution of 1.46 g. (0.021 mole) of sodium nitrite in 15 ml. of water until a drop of the solution immediately colored cadmium iodide-

starch paper a pale blue.

This ice-cold benzenediazonium chloride solution was added to the cold, stirred, alkaline solution of the phenol at such a rate that the temperature did not rise above 5°. A beautiful orange precipitate formed at once. After addition was complete, the reaction mixture was stirred for forty-five minutes, and the coupling product filtered off and dried. Two crystallizations from alcohol yielded rust-colored needles of 1-benzeneazo-4-hydroxy-6-methoxydibenzofuran, m. p. 175°. The yield was 3.6 g. or 56.6%.

Anal. Calcd. for $C_{19}H_{14}O_3N_2$: N, 8.84. Found: N, 8.89.

Methylation of 1-Benzeneazo-4-hydroxy-6-methoxydibenzofuran

To a refluxing, stirred solution of 1.59 g. (0.005 mole) of 1-benzeneazo-4-hydroxy-6-methoxydibenzofuran and 4.77 g. (0.0378 mole) of dimethyl sulfate in 10 ml. of acetone was added dropwise a solution of 6.35 g. (0.113 mole) of potassium hydroxide in 5 ml. of water. Heating and stirring were continued for thirty minutes after addition was complete. The 250 ml. reaction flask was nearly filled with water, and the orange 1-benzeneazo-4,6-dimethoxydibenzofuran, m. p. 169-170°, was filtered off. The yield was 1.46 g. or 88%. The compound crystallized from benzene in the form of beautiful deep orange prisms, m. p. 170°. The needles which first appeared in the

hot solvent always changed to the prismatic form as the benzene gradually cooled.

Anal. Calcd. for $C_{20}H_{16}O_3N_2$: N, 8.44. Found: N, 8.51.

Reduction of 1-Benzeneazo-4,6-dimethoxydibenzofuran

The procedure used by Mrs. VanEss (8) to reduce 1-benzeneazo-4-hydroxydibenzofuran was adopted.

One gram (0.003 mole) of 1-benzeneazo-4,6-dimethoxydibenzofuran was dissolved in 40 ml. of boiling acetic acid. To this hot solution was added gradually a solution of 2.0 g. of stannous chloride hydrate in 15 ml. of concentrated hydrochloric acid. The color of the reaction mixture quickly changed from orange to dark red, and further heating soon dispelled all color. During the night, a white complex tin salt of the amine crystallized out. Therefore, in order to liberate the amine, the solution was cooled in an ice bath and 30% sodium hydroxide was added until the precipitated tin hydroxide had redissolved. The solution was then made acid with hydrochloric acid, and, finally, slightly basic with ammonium hydroxide. The liberated amine was extracted with ether, the ether solution was dried over sodium sulfate, and the amine hydrochloride was precipitated with gaseous hydrogen chloride. An aqueous solution of the hydrochloride, subsequent to Norite treatment and filtration, was decomposed

with ammonium hydroxide. This authentic 1-amino-4,6-dimethoxydibenzofuran crystallized from methanol in the form of small pale purple needles, m. p. 162-162.5°. The yield was 0.24 g. or 32.8% of the theoretical.

Anal. Calcd. for $C_{14}H_{15}O_5N$: N, 5.77. Found: N, 5.88.

Hydrolysis of 1-Acetamino-4,6-dimethoxydibenzofuran

Two grams (0.007 mole) of 1-acetamino-4,6-dimethoxydibenzofuran was refluxed for eight hours in a solution consisting of 50 ml. of concentrated hydrochloric acid and 200 ml. of alcohol. Small very pale pink needles of 1-amino-4,6-dimethoxydibenzofuran hydrochloride, m. p. 286-287°, were filtered from the cooled solution. The yield was 1.85 g. or 94.5%.

Two-tenths of a gram of the hydrochloride was dissolved in hot water, and the free amine, m. p. 161.5-162°, was liberated by the addition of ammonium hydroxide. Recrystallization from methanol with Norite treatment raised the melting point to 162-162.5°.

This amine and authentic 1-amino-4,6-dimethoxydibenzofuran, prepared by the reduction of 1-benzeneazo-4,6-dimethoxydibenzofuran, were proved identical by means of a mixed melting point determination.

Amination of 1-Bromo-3,4-dimethoxydibenzofuran

An intimate mixture of 7.5 g. (0.0244 mole) of 1-bromo-3,4-dimethoxydibenzofuran, 15.0 g. of powdered cuprous bromide, and 130 ml. of concentrated ammonium hydroxide was heated in an electrically heated bomb for fourteen and one-half hours at a temperature of 220-230°.

The contents of the cooled bomb were extracted five times with a total volume of nearly 600 ml. of ether. This solution of the amine was dried overnight over sodium sulfate. Gaseous hydrogen chloride precipitated the amine hydrochloride from the filtered ether solution. The crude hydrochloride was dissolved in hot water, and the solution was digested with Norite and filtered. Ammonium hydroxide precipitated 0.6 g., a 10.1% yield, of pale purple 1-amino-3,4-dimethoxydibenzofuran, m. p. 162.5-163°. Needles which crystallized from dilute methanol possessed an unaltered melting point.

Anal. Calcd. for $C_{14}H_{13}O_3N$: N, 5.76. Found: N, 5.94.

Hydrolysis of 1-Acetamino-3,4-dimethoxydibenzofuran

A combination of 1.6 g. (0.0056 mole) of 1-acetamino-3,4-dimethoxydibenzofuran, 50 ml. of alcohol, and 5.0 g. of potassium hydroxide was refluxed in a sand bath for two hours. Dilution with 400 ml. of water precipitated shiny plates

which were filtered off and crystallized, following brief Norite treatment, from dilute methanol. The lustrous white needles of 1-amino-3,4-dimethoxydibenzofuran, m. p. 162.5-165°, were tinted purple in contact with the atmosphere. The yield was 0.65 g. or 47.6% of the theoretical.

A mixed melting point determination with authentic 1-amino-3,4-dimethoxydibenzofuran prepared by amination of 1-bromo-3,4-dimethoxydibenzofuran established the identity of the two amines.

Preparation of 1,3,9-Tribenzeneazo-4,6-dimethoxydibenzofuran

A solution of 6.0 g. (0.03 mole) of 4,6-dihydroxydibenzofuran in 45 ml. of 15% potassium hydroxide was diluted with 90 ml. of water and placed in a 500 ml. flask equipped with stirrer, low-temperature thermometer, and dropping funnel. This solution was then cooled to 2° by immersion in an ice-salt bath.

The diazonium salt solution was prepared as follows: To an ice-cold solution of 7.75 g. (0.06 mole) of aniline hydrochloride in 25 ml. of water was added ca. 45 g. of finely cracked ice and 10.1 ml. of concentrated hydrochloric acid. Then a solution of sodium nitrite, prepared from 4.38 g. (0.063 mole) of the salt in 25 ml. of water, was poured down the side of the beaker until a drop of the well stirred, ice-cold solution immediately developed a distinct blue spot on cadmium iodide-starch paper.

This diazonium salt solution, cooled to 0°, was trickled down the side of the flask containing the cold, stirred alkaline solution of the phenol at such a rate that the temperature did not exceed 5°. Mechanical stirring was continued for thirty minutes, after which the reaction mixture was acidified and the very dark brown solid filtered off. Crystallization from acetic acid produced 5.1 g. of very dark brown microcrystalline material, m. p. ca. 224° with decomposition. Recrystallization from the same solvent, attended by considerable loss due to resinification, raised the melting point to 228° with decomposition. Micro-Dumas analyses revealed that this substance, which dissolved in acetone with the formation of a brilliant red color, was, actually, a tribenzeneazo derivative, i. e., 1,3,9-tribenzeneazo-4,6-dihydroxydibenzofuran. Inasmuch as the nitrogen values were nearly 1% low, it was assumed that the impurity was the dibenzeneazo derivative.

Methylation imparted stability to the molecule, and a pure compound was isolated by the following procedure: To a refluxing, stirred solution of 2.11 g. (0.0041 mole) of impure 1,3,9-tribenzeneazo-4,6-dihydroxydibenzofuran, 9.5 g. (0.075 mole) of dimethyl sulfate, and 20 ml. of acetone was slowly added a solution of 12.9 g. (0.23 mole) of potassium hydroxide in 10 ml. of water. Refluxing and stirring were continued for twenty-five minutes after the alkali had been introduced.

Following dilution with 500 ml. of water, 2.2 g. of the red-orange product, m. p. 184-186°, was filtered off. Crystallization from acetic acid secured 1.71 g. (76.6%) of 1,3,9-Tribenzeneazo-4,6-dimethoxydibenzofuran, m. p. 191-195°. Recrystallization did not sharpen the melting point.

Anal. Calcd. for $C_{32}H_{24}O_3N_6$: N, 15.56. Found: N, 15.52.

Oxidation of 1-Acetyl-4,6-dimethoxydibenzofuran

In accordance with the procedure of Fuson and Tullock (105), 1.0 g. (0.0057 mole) of 1-acetyl-4,6-dimethoxydibenzofuran was dissolved in 50 ml. of dioxane, 5 ml. of 10% sodium hydroxide was added, and iodine-potassium iodide solution was slowly introduced with shaking until iodine color persisted after the solution had been heated to 60° for two minutes. The dark color of the excess iodine was removed with 10% sodium hydroxide solution, the reaction mixture was diluted to a volume of 375 ml., and the precipitated iodoform filtered off. The filtrate was heated to boiling, acidified with dilute sulfuric acid, cooled, and the white acid removed by filtration. Crystallization from acetic acid produced authentic 4,6-dimethoxy-1-dibenzofurancarboxylic acid, m. p. 297-298°. The yield was 0.55 g. or 55.2% of the theoretical.

(105) Fuson and Tullock, J. Am. Chem. Soc., 56, 1638 (1934).

Anal. Calcd. for $C_{12}H_{12}O_5$: C, 66.45; H, 4.45. Found: C, 66.21; H, 4.53.

Carbonation of 4,6-Dimethoxy-1-dibenzofurylmagnesium Bromide

Into a dry 500 ml. flask equipped with mechanical stirrer and Hopkin's condenser was placed a solution of 22.5 g. (0.073 mole) of 1-bromo-4,6-dimethoxydibenzofuran in 300 ml. of anhydrous benzene-ether (1:1 by volume). After 2.0 g. (0.082 mole) of magnesium ribbon had been introduced and a nitrogen atmosphere provided, the reaction was initiated by the addition of the reaction product obtained from heating a crystal of iodine with a few magnesium filings. The reaction mixture was vigorously refluxed and stirred for a six-hour interval. Carbonation was accomplished by filtering the Grignard solution under an atmosphere of nitrogen into a large excess of solid carbon dioxide.

After standing overnight, the product was hydrolyzed with ice and hydrochloric acid, and the white solid was filtered from solution. The benzene-ether layer was extracted twice with 10% sodium hydroxide solution. The alkaline extract was added to the solid, contained in a two-liter beaker, and 5% sodium hydroxide was introduced until the beaker was two-thirds full. The solution was heated to boiling, filtered, and acidified with hydrochloric acid. The white amorphous acid obtained by filtration crystallized from acetic acid in the form of very small needles, m. p. 297-298°.

No depression in melting point was observed when this acid was mixed with authentic 4,6-dimethoxy-1-dibenzofurancarboxylic acid secured by oxidation of 1-acetyl-4,6-dimethoxydibenzofuran. A mixed melting point determination involving the corresponding methyl esters confirmed the identity of the two acids.

Preparation of Methyl 4,6-Dimethoxy-1-dibenzofurancarboxylate

An excess of diazomethane in ether, prepared from ethyl N-nitroso-N-methyl-carbamate by the method of v. Pechmann (106), was poured on 1.0 g. (0.0037 mole) of 4,6-dimethoxy-1-dibenzofurancarboxylic acid. Dioxane was added with shaking until all of the acid had dissolved. The reaction mixture was allowed to stand overnight, the ether was evaporated, and the hot dioxane solution was diluted to incipient turbidity with water. The solution was clarified with dioxane, cooled slowly, and the white crystals were filtered off. Nearly a quantitative yield of methyl 4,6-dimethoxy-1-dibenzofurancarboxylate, m. p. 163°, was obtained.

Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.11; H, 4.93. Found: C, 67.2; H, 5.11.

(106) v. Pechmann, Ber., 28, 855 (1895).

Preparation of Diazomethyl 4,6-Dimethoxy-1-dibenzofuryl Ketone

Parker, applying the discovery of Arndt and Eistert (107) to dibenzofuran chemistry, synthesized 4-dibenzofurylacetamide from 4-dibenzofurancarboxylic acid by rearrangement of diazomethyl 4-dibenzofuryl ketone. The succeeding three preparations, which collectively constitute a synthetic route to 4,6-dimethoxy-1-dibenzofurylacetic acid, are based on procedures described by Parker (13).

The required acid chloride was prepared by refluxing 11.5 g. (0.042 mole) of 4,6-dimethoxy-1-dibenzofurancarboxylic acid with 80.0 g. (0.672 mole) of thionyl chloride for two and one-half hours, during which time the solid acid slowly dissolved to produce a clear red solution. The excess thionyl chloride was distilled off at diminished pressure at a temperature of 100° (water bath). The crude pink acid chloride, after crystallization from dry benzene, melted over a wide, indefinite range which indicated incomplete conversion. Purification was effected by boiling the substance with petroleum ether (b. p. 77-115°). The acid chloride dissolved, and 5.2 g. of impure, unconverted acid was removed by filtration. The colorless product which separated from the cooled solution melted at 147-150°. The yield was 6.2 g. or 50.5% of the theoretical. (Perchance phosphorus penta-

(107) Arndt and Eistert, Ber., 68, 200 (1935).

chloride would furnish superior yields). This acid chloride was not further purified or analyzed, but used directly in the following procedure.

The diazomethane prepared from 20 ml. of ethyl N-nitroso-N-methylcarbamate by the method of v. Pechmann (106), dissolved in 200-225 ml. of anhydrous ether, was placed in a one-liter, three-necked flask immersed in an ice bath and equipped with a mechanical stirrer. To the efficiently stirred solution was introduced, in several portions, 6.2 g. (0.0213 mole) of 4,6-dimethoxy-1-dibenzofurancarboxylic acid chloride. After five minutes of stirring, 100 ml. of anhydrous dioxane was added to effect solution. The ice bath was removed and the clear yellow reaction mixture was allowed to stand overnight.

The next morning, pure, pale yellow crystals of diazomethyl 4,6-dimethoxy-1-dibenzofuryl ketone, m. p. 151° with gas evolution, were filtered from solution. The yield was 1.34 g. or 21.2% of the theoretical.

Anal. Calcd. for $C_{16}H_{12}O_4N_2$: N, 9.46. Found: *N, 9.51.

By removing the solvent at diminished pressure, 4.75 g. of substance, presumably the crude diazomethyl ketone, was obtained. However, an attempt to secure crystalline material from petroleum ether (b. p. 77-115°) was unsuccessful, resinous substances

* The author is grateful to Mr. L. D. Apperson for this micro-Dumas analysis.

being formed. Probably thermal decomposition of the ketone had taken place.

Preparation of 4,6-Dimethoxy-1-dibenzofurylacetamide

A solution of 1.25 g. (0.0042 mole) of diazomethyl 4,6-dimethoxy-1-dibenzofuryl ketone in 75 ml. of dioxane was placed in a 250 ml. flask fitted with reflux condenser and mechanical stirrer. With efficient stirring, 15 ml. of concentrated ammonium hydroxide was added followed by 5 ml. of 10% silver nitrate solution. Heating on the steam bath and stirring were continued for forty-five minutes. Then 5 ml. more of concentrated ammonium hydroxide was added, and the stirred solution was heated for thirty minutes longer.

The hot solution was filtered and diluted to a volume of 300 ml. with water. Cooling in the refrigerator precipitated the gray amide, m. p. 206-207°. It weighed 0.82 g. (66.6%). Pure 4,6-dimethoxy-1-dibenzofurylacetamide crystallized from alcohol, after digestion with Norite, in the form of white rosettes of lustrous needles, m. p. 210-211°. The yield of pure compound was 0.62 g. or 51.6% of the theoretical.

Anal. Calcd. for $C_{16}H_{15}O_4N$: N, 4.91. Found: N, 4.86.

Preparation of 4,6-Dimethoxy-1-dibenzofurylacetic Acid

A mixture of 0.5 g. (0.00175 mole) of 4,6-dimethoxy-1-dibenzofurylacetamide, 25 ml. of 15% sodium hydroxide solution and 5 ml. of alcohol was refluxed for thirteen hours before a clear solution was realized. The reaction mixture was diluted with 50 ml. of water, gently boiled with a pinch of Norite, and filtered. Acidification of the solution precipitated the crude acid in nearly quantitative yield, m. p. 204-205°. Two crystallizations from alcohol furnished colorless needles of 4,6-dimethoxy-1-dibenzofurylacetic acid, m. p. 205.5-206.5°. The yield was 0.36 g. or 71.7% of the theoretical.

Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.11; H, 4.93. Found: C, 67.0; H, 4.98.

Attempted Cyclization of 1-Acetamino-4,6-dimethoxydibenzofuran by the Bischler-Napieralski Reaction

A. Employing essentially the procedure developed by Morgan and Walls for the preparation of 9-substituted phenanthridine derivatives (82), 1.43 g. (0.005 mole) of 1-acetamino-4,6-dimethoxydibenzofuran was gently refluxed with 6.0 g. of freshly distilled phosphorus oxychloride over a period of an hour. After pouring the product in 25 ml. of water, the delayed hydrolysis suddenly became so violent that ice was added. Enough water was then added to make the total volume 100 ml., whereupon the solution

was heated to boiling and filtered. Addition of ammonium hydroxide to the filtrate precipitated an inappreciable amount of white, flocculent substance. No starting material was recovered from the amorphous residue.

B. In accordance with the method utilized by Pictet and Gams (83) for the synthesis of papaverine, 1.0 g. of 1-acetamino-4,6-dimethoxydibenzofuran was dissolved in 80 ml. of dry xylene in a 250 ml. flask equipped with stirrer and reflux condenser. To the refluxing solution was added 2.0 g. of phosphorus pentoxide. Refluxing and efficient stirring were continued for five minutes. The reaction mixture was then cooled in an ice bath and cautiously hydrolyzed with ice and molar hydrochloric acid. The contents of the flask were poured into a beaker, warmed on the hot plate, and filtered. The xylene layer was removed, and the aqueous layer was extracted with ether to remove residual xylene. The water layer was then rendered strongly basic with 10% sodium hydroxide solution and extracted twice with a total volume of 150 ml. of ether which was dried over sodium sulfate, filtered and evaporated. About fifty milligrams of discolored, basic solid, m. p. 184-214°, were thus secured. Owing to the minute quantity of such crude material, further investigation of the substance was deemed inexpedient.

In another experiment involving the same apparatus and procedure, a solution of 1.0 g. of 1-acetamino-4,6-dimethoxy-

dibenzofuran in 80 ml. of anhydrous ether was vigorously refluxed with a suspension of 5.0 g. of phosphorus pentoxide for fifteen minutes. Not a trace of basic material could be isolated.

Attempted Cyclization of 4,6-Dimethoxy-1-dibenzofurylacetic Acid

A mixture of 0.30 g. (0.0011 mole) of 4,6-dimethoxy-1-dibenzofurylacetic acid and 0.3 g. (0.0017 mole) of phosphorus pentachloride contained in a stoppered 10 ml. Claisen flask was warmed gently in a smoky flame until solution had been effected. During this operation, moisture was excluded by means of a calcium chloride tube connected to the side arm of the flask. The phosphorus oxychloride and excess phosphorus pentachloride were removed by vacuum distillation at a temperature of 100°. (flask immersed in boiling water).

An ice-cold solution of 0.3 g. of anhydrous aluminum chloride in 5 ml. of dry nitrobenzene was added to the cold acid chloride. The solution immediately turned a deep blue color. After being frequently shaken in the ice bath for thirty minutes, the reaction mixture was allowed to stand at room temperature for twenty hours.

The blue-green reaction product was hydrolyzed in a 200 ml. round-bottomed flask containing ice and hydrochloric acid, and the nitrobenzene was removed by steam distillation. The pulverized residue was boiled with 10% sodium hydroxide solution

and filtered. No starting material was obtained from the acidified filtrate. The brown residue was extracted with a large volume of ether. The ether solution was dried with sodium sulfate and filtered. Removal of the solvent left an oil which could not be crystallized. No pure organic material could be isolated from the ether-insoluble residue.

D I S C U S S I O N

Attempts to Bridge the 1- and 9-Positions in Dibenzofuran Derivatives. Several attempts to prepare a phenanthrylene oxide derivative by intramolecular alkylation of 1-chloroacetyl-4-methoxydibenzofuran in the presence of aluminum chloride emphasized the noteworthy inertness of the chlorine atom under the conditions of the Friedel-Crafts reaction. Despite variation in solvent and temperature conditions, not a trace of the desired compound or of even the possible intermolecular reaction product was found. In every case either the starting material was recovered or hopeless decomposition took place. It is of interest to note that the halogen atom in ethyl chloroacetate behaves in a similar manner. Calloway (108) was unable to alkylate methyl 2-furoate with ethyl chloroacetate in the presence of aluminum chloride.

The isolation of bi-(4-methoxy-1-dibenzofuroyl) from the Friedel-Crafts reaction of 4-methoxydibenzofuran with oxalyl chloride suggested that in order to realize the formation of the desired o-quinone with oxalyl chloride, both the 1- and 9-positions of the dibenzofuran nucleus should be activated by the introduction of suitable substituents in the 4- and 6-positions. Consequently, 4,6-dimethoxydibenzofuran was prepared and subjected to the

(108) Calloway, Doctoral Dissertation, Iowa State College, 1933, p. 87.

Friedel-Crafts reaction with oxalyl chloride. Again intermolecular condensation proceeded with the formation of bi-(4,6-dimethoxy-1-dibenzofuroyl) in excellent yield. Although both carbon disulfide and nitrobenzene were employed as solvents, not a trace of the o-quinone could be isolated.

Likewise, failure attended three efforts to synthesize a 4,5-phenanthridine oxide derivative from 1-acetamino-4,6-dimethoxydibenzofuran by application of the Bischler-Napieralski reaction (80). In retrospect it is thought that probably the imposed conditions were too drastic. In light of Schlittler's synthesis of pukateine (86), phosphorus pentachloride in cold chloroform offers possibilities.

The recent synthesis of 4,6-dimethoxy-1-dibenzofurylacetic acid has supplied a compound which holds unprecedented promise of yielding a 4,5-phenanthrylene oxide derivative. One unsuccessful preliminary attempt to achieve ring closure has been described. Again, it is probable that the conditions adopted were too harsh. Thionyl chloride, employed, for example, in the synthesis of Diel's Hydrocarbon (109), might yield a purer acid chloride, and thirty minutes at 0° for the Friedel-Crafts reaction, the optimum conditions for Weitzenböck's synthesis (73) of 1,6-dihydroxypyrene, would possibly afford ample reaction time. Mild

(109) Hilleman, Ber., 69, 2610 (1936).

conditions were provided by Bachmann and Kloetzel (110) for the intramolecular condensation of phenanthrylpropionic acids.

Cumulative evidence supports the idea that the 4,5-phenanthrylene oxide nucleus is subjected to considerable strain. Raman spectral studies (111) indicate that the benzene rings in the dibenzofuran molecule are distorted. Although a goodly number of dehydrating agents were investigated, Schmidt and Kämpf (112) were unable to synthesize a 4,5-phenanthrylene oxide quinone from 4,5-dihydroxyphenanthrenequinone by ring closure. Whereas a temperature of 400° is required to prepare o-biphenol from dibenzofuran, Vongerichten and Dittmer (113) have demonstrated that the oxygen bridge in morphenol can be cleaved by fusion with potassium hydroxide at 250°.

Metalation. The selective metalation of N-ethylcarbazole (111) classically demonstrates that the particular nuclear hydrogen replaced depends on the nature of the metal which is introduced. From extensive metalation studies in this laboratory (14, 15, 55, 114, 115, 17), the following generalization has been

(110) Bachmann and Kloetzel, J. Am. Chem. Soc., 59, 2207 (1937).
(111) Donzelot and Chaix, Compt. rend., 202, 851 (1936).
(112) Schmidt and Kämpf, Ber., 36, 3745 (1903).
(113) Vongerichten and Dittmer, Ber., 39, 1718 (1906).
(114) Gilman and Kirby, J. Org. Chem., 1, 146 (1936).
(115) Jacoby, Doctoral Dissertation, Iowa State College, 1938.

formulated: All aromatic polynuclear compounds possessing either ether or tertiary amino substituents can be metalated with ease by organoalkali compounds, and, in every case, the entering alkali metal will replace a nuclear hydrogen ortho to those substituents.

Dibenzofuran is metalated exclusively in positions ortho to the diphenyl ether bridge (15). Bebb has shown (55) that the 1- and 3-positions are involved when 2-methoxydibenzofuran is metalated by means of organolithium compounds. Metalation of 4-methoxydibenzofuran (17) with n-butyllithium substitutes the 3- and 6-positions, the two isomers being formed in almost equal quantity. A hydrogen vicinal to the oxygen atom in diphenyl ether is replaced by metal when n-butyllithium is employed as the metalating agent (116). Dibenzothiophene (112) and 5-ethylcarbazole (114) are metalated exclusively in the 4-positions (ortho to the thio ether and tertiary amino linkages, respectively) by organoalkali compounds. Examples could be multiplied; in short, no exceptions to this generalization are known.

In light of this rule, it is reasonable to predict that isomers, 3,4-dimethoxy-2-dibenzofuryllithium and 3,4-dimethoxy-6-dibenzofuryllithium, would be formed if 3,4-dimethoxydibenzofuran were metalated with n-butyllithium. Conversely, an excellent

(116) Unpublished work by Mr. W. H. Harber.

yield of one product, 4,6-dimethoxy-3-dibenzofuryllithium, could be expected if 4,6-dimethoxydibenzofuran were subjected to the influence of the same metalating agent. Furthermore, providing that two equivalents of n-butyllithium were employed, it might be possible to dimetalate the hetero-substituted 4,6-dimethoxydibenzofuran to realize 3,7-dilithio-4,6-dimethoxydibenzofuran, for 2,2'-dimethoxybiphenyl has been dimetalated in 50% yield (117) under similar conditions.

Apparently, there is no satisfactory explanation for the powerful ortho-orienting influence exerted by ether and tertiary amino groups in organoalkali metalations. It has been suggested that metalation is a function of the acidity of the hydrogen replaced (118) (119). The fact that the same hydrogen of an aromatic cycle is not always replaced by any metal (114) is an apparent contradiction to this idea. Mr. Henry Pacevitz of this laboratory has made the interesting observation that a vinylogous system is involved.

The Coupling of Organoalkali Compounds. The unexpected isolation of bi-(6-methoxy-4-dibenzofuryl) following metalation of 4-methoxydibenzofuran with subsequent oxidation of the metalation product justified an explanation for the mechanism of this

(117) Unpublished work by the author.
(118) Conant and Wheland, J. Am. Chem. Soc., 54, 1212 (1932).
(119) Gilman and Breuer, ibid., 56, 1123 (1934).

definitely established coupling reaction. Furthermore, subsequent to this discovery, an investigation of the ether solution remaining from the metalation of dibenzofuran followed by oxidation of the product disclosed the presence of bi-(4-dibenzofuryl) in considerable quantities. Therefore, this coupling reaction appeared to be quite general.

It is not unreasonable to conclude that the coupling proceeds during the oxidation of the organolithium compound, lithium peroxide being the other product formed, for search of the literature revealed that Wooster (120) has reported an analogous reaction of an organosodium compound. When dry air was passed through a liquid ammonia solution of diphenylmethylsodium, tetraphenylethane and sodium peroxide were the products obtained. Wooster has concluded that ..."the formation of an organic peroxide as an oxidation product is typical only of those organoalkali compounds which are derivatives of free radicals."

Since convincing evidence has been presented for the intermediate formation of organic peroxides during the oxidation of aryl Grignard reagents (121) (94), the suggested mechanism for the coupling reaction of these organolithium compounds is all the more plausible. The possibility that coupling proceeds prior to oxidation could be readily investigated by carbonation of the

(120) Wooster, Chem. Rev., 11, 21 (1932).
(121) Porter and Steel, J. Am. Chem. Soc., 42, 2650 (1920).

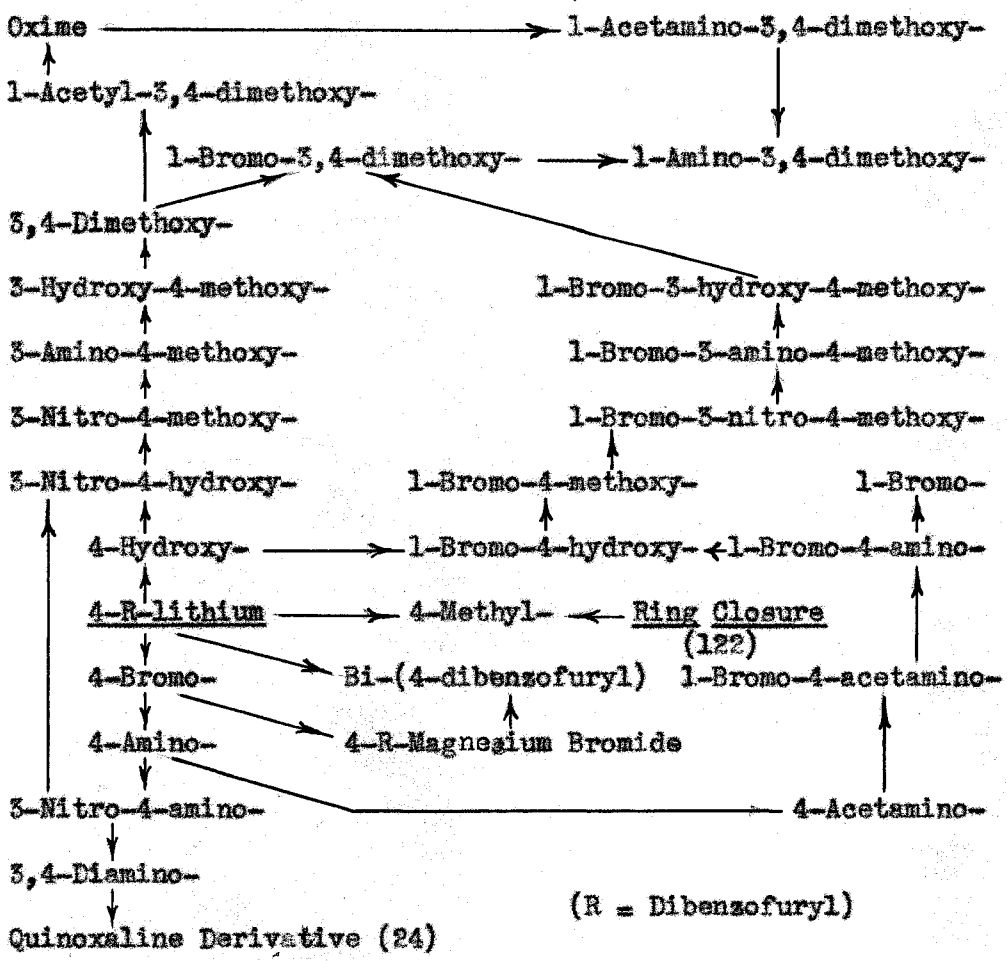
organolithium compound. Assuming that molecular oxygen is the agent responsible for the coupling, certain questions arise. Does oxygen play a role in the Wurtz-Fittig reaction? Perhaps that well known reaction would proceed more smoothly at lower temperature under a pressure of oxygen.

Evidence for the Assigned Structures. Diagram I pictorially presents the transformations which have been conducted in order to elucidate the structures of all homonuclear-substituted dibenzofuran derivatives described in this dissertation. By fusing 2,2'-dihydroxy-3-methylbiphenyl with zinc chloride, Kruber (122) accomplished a ring closure to obtain authentic 4-methyldibenzofuran which was subsequently oxidized to 4-dibenzofurancarboxylic acid. The acid realized by carbonating the monometalation product of dibenzofuran (14) was shown to be identical, thus proving that metalation had occurred in the 4-position.

4-Acetaminodibenzofuran (Table I) prepared from 4-dibenzofuryllithium was nitrated, the nitro group of the hydrolyzed product melting at 185-186° was catalytically reduced, and the resulting diamine was reacted with 9,10-phenanthrenequinone to produce a quinoxaline derivative (24), thus unequivocally demonstrating that the nitro group had entered the 3-position. 4-Hydroxydibenzofuran was likewise mononitrated (18), and Jacoby proved this compound to be 3-nitro-4-hydroxydibenzofuran by

DIAGRAM I.

TRANSFORMATIONS OF HOMONUCLEAR DIBENZOFURANS



(122) Kruber, Ber., 65, 1382 (1932).

preparing the identical compound from a sample of Swislowsky's established 3-nitro-4-aminodibenzofuran.

Through the kindness of Mr. A. L. Jacoby, a sample of 3-amino-4-methoxydibenzofuran, prepared from 3-nitro-4-hydroxydibenzofuran, was obtained. In turn, this compound was transformed into authentic 3-hydroxy-4-methoxydibenzofuran, which did not depress the melting point of the isomer of 4-hydroxy-6-methoxydibenzofuran isolated after the metalation product of 4-methoxydibenzofuran had been oxidized.

P. R. VanEss (9) established that 4-acetaminodibenzofuran oriented bromine to the 1-position by deacetylation followed by removal of the amino group to obtain a monobromodibenzofuran which proved to be different from the known 2-, 3-, and 4-bromodibenzofurans. Authentic 1-bromo-4-hydroxydibenzofuran prepared from 1-bromo-4-aminodibenzofuran and the product secured by direct bromination of 4-hydroxydibenzofuran were shown to be identical. Since amino and hydroxyl groups activate the ortho and para positions of an aromatic cycle to a remarkable degree, the possibility that the 9-positions of 4-acetamino- and 4-hydroxydibenzofuran were substituted is considered very remote.

Parker (13) discovered that 4-methoxydibenzofuran oriented bromine to the 1-position by comparison of the product with a known specimen (9). Later, he proved that the mononitration product of 1-bromo-4-methoxydibenzofuran was 1-bromo-3-nitro-4-

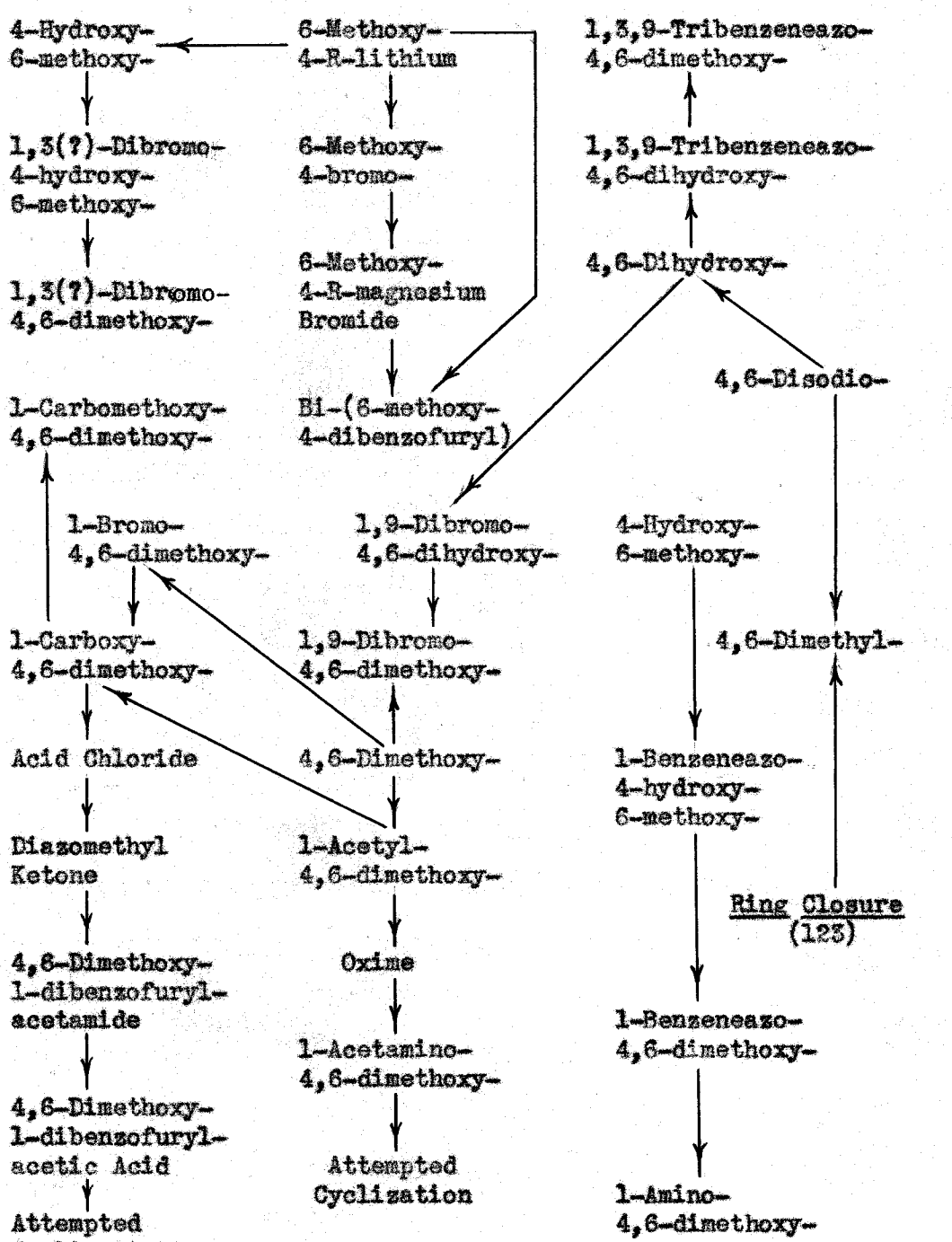
methoxydibenzofuran by simultaneous reduction and dehalogenation. An intimate mixture of the product and authentic 3-amino-4-methoxydibenzofuran exhibited no depression in melting point (13).

Direct acetylation and bromination of 3,4-dimethoxydibenzofuran were shown to involve the 1-position by the following sequence of reactions (17): A sample of 1-bromo-3-nitro-4-methoxydibenzofuran, kindly furnished by Mr. P. T. Parker, was reduced according to his directions (13) to the corresponding amine. This 1-bromo-3-amino-4-methoxydibenzofuran was transformed, through the diazonium salt, to authentic 1-bromo-3-hydroxy-4-methoxydibenzofuran. The identical compound was secured by the direct bromination of 3-hydroxy-4-methoxydibenzofuran. Methylation of 1-bromo-3-hydroxy-4-methoxydibenzofuran produced the same compound as that obtained in excellent yield by direct bromination of 3,4-dimethoxydibenzofuran. Acetylation of 3,4-dimethoxydibenzofuran was also shown to substitute the 1-position by the following series of reactions: The corresponding oxime was converted to the acetamino derivative by means of the Beckmann rearrangement. Subsequent hydrolysis secured an amine identical with authentic 1-amino-3,4-dimethoxydibenzofuran prepared by direct amination of 1-bromo-3,4-dimethoxydibenzofuran.

Bi-(4-Dibenzofuryl) was synthesized by coupling 4-dibenzofurylmagnesium bromide by means of anhydrous cupric chloride.

DIAGRAM II.

TRANSFORMATIONS OF HETERONUCLEAR DIBENZOFURANS



(123) Sugii and Shindo, J. Pharm. Soc. Japan, 54, 149 (1934).

The identical compound was isolated from the reaction mixture resulting from the oxidation of 4-dibenzofuryllithium.

Diagram II schematically illustrates the interrelationships of the heteronuclear dibenzofurans described in this thesis. The following evidence, admittedly indirect, is presented to reveal the bases for the assigned structures.

An excellent yield of monobenzeneazo-4-hydroxy-6-methoxydibenzofuran was obtained by coupling the definitely established 4-hydroxy-6-methoxydibenzofuran (15) with benzenediazonium chloride. By analogy with all known cases of coupling by phenols and naphthols under similar conditions (124), it was assumed the benzeneazo group entered the 1-position, for only when the para position is blocked or when the reaction medium is strongly basic does ortho coupling take place to any appreciable extent. The possibility that the position para to the phenolic ether group (9-position) was involved in the coupling reaction can be definitely excluded, for phenolic ethers, like hydrocarbons, afford coupling products only under exceptional conditions or with negatively substituted diazo-compounds. Then, too, when coupling does take place, it is notable that the alkyl group of the phenolic ether is partially or completely removed in the process (125).

(124) Saunders, "The Aromatic Diazo-Compounds and Their Technical Applications", Edward Arnold & Co., London, 1936, pp. 104 et. seq.
(125) Auwers and Michaelis, Ber., 47, 1281 (1914).

Furthermore, amines are classed next to phenols and naphthols with respect to ease of coupling, and 2-aminodibenzofuran would not couple with benzenediazonium chloride (8) under conditions which quantitatively coupled β-naphthylamine (126). Moreover, Mrs. VanEss (8) proved that 4-hydroxydibenzofuran readily coupled to form 1-benzeneazo-4-hydroxydibenzofuran. These accumulated considerations offered convincing evidence that the coupling product was, indeed, 1-benzeneazo-4-hydroxy-6-methoxy-dibenzofuran. Methylation of this product followed by reduction produced 1-amino-4,6-dimethoxydibenzofuran.

Acetylation of 4,6-dimethoxydibenzofuran was proved to involve the 1-position by preparation of the corresponding oxime, which was subjected to the Beckmann rearrangement. Deacetylation of the reaction product yielded 1-amino-4,6-dimethoxydibenzofuran.

A Grignard reagent was prepared from the monobromination product of 4,6-dimethoxydibenzofuran, and subsequent carbonation furnished an acid which proved to be 4,6-dimethoxy-1-dibenzo-furancarboxylic acid, identical with the authentic acid obtained by subjecting 1-acetyl-4,6-dimethoxydibenzofuran to the haloform oxidation. Thus, monobromination was proved to substitute the 1-position.

Instead of the expected 1,9-dibenzeneazo-4,6-dihydroxy-dibenzofuran, an impure tribenzeneazo-4,6-dihydroxydibenzofuran

(126) Bamberger and Schieffelin, Ber., 22, 1376 (1889).

was obtained when 4,6-dihydroxydibenzofuran was treated with two equivalents of benzenediazonium chloride. Methylation and recrystallization resulted in the isolation of a pure compound, the structure of which, on the basis of analogy, is very probably 1,3,9-tribenzeneazo-4,6-dimethoxydibenzofuran.

Dibromination of 4,6-dihydroxydibenzofuran with subsequent methylation produced the same compound as that obtained by the direct dibromination of 4,6-dimethoxydibenzofuran. Inasmuch as it is known with certainty that 4-methoxydibenzofuran orients bromine to the 1- or 9-position and that 4,6-dimethoxydibenzofuran is very probably substituted in the 1-position when one equivalent of bromine is employed, it is reasonable to conclude, especially when one considers the symmetry of the molecule, that these two dibromo compounds are 1,9-dibromo-4,6-dihydroxy- and 1,9-dibromo-4,6-dimethoxydibenzofuran, respectively.

Dibromination of 4-hydroxy-6-methoxydibenzofuran followed by methylation produced a dibromo-4,6-dimethoxydibenzofuran which, quite unexpectedly, proved to be dissimilar from the one obtained by direct dibromination of 4,6-dimethoxydibenzofuran. Presumably, the hydroxyl group in 4-hydroxy-6-methoxydibenzofuran activates the ring in which it is located to such a degree that homonuclear disubstitution takes place with the formation of the assigned structure, 1,3-dibromo-4-hydroxy-6-methoxydibenzofuran. Perhaps 1-hydroxy-8-methoxynaphthalene would

dibrominate in an analogous manner.

Had the indicated cyclization attempts (Diagram II) proved successful the case for 1,9-disubstitution would have been absolute.

The Bucherer Reaction. The favorable yield of 4,6-diaminodibenzofuran from 4,6-dihydroxydibenzofuran stresses the synthetic possibilities of the Bucherer reaction (102) (103) in dibenzofuran chemistry. Furthermore, in some transformations involving structural proof it may be desirable to remove hydroxyl groups from the molecule. Whereas the direct elimination of an hydroxyl group is, ordinarily, a hazardous undertaking, an amino group, by conversion to its diazonium salt, can be removed with favorable consequences.

The Beckmann Rearrangement. On the basis of Meisenheimer's proof of the interchange of the hydroxyl group and the trans group in the Beckmann rearrangement of oximes (127), experiment has demonstrated that the 4-methoxy-1-dibenzofuryl and 4,6-dimethoxy-1-dibenzofuryl groups in the corresponding acetyl oximes orient themselves predominantly, if not exclusively, trans with respect to the hydroxyl group. Consequently, this reaction has proved the best known method of introducing an acetamino

(127) Meisenheimer and co-workers, Ber., 54, 3206 (1921); Ann., 495, 249 (1932).

group in the 1-position of 4,6-dimethoxydibenzofuran. Therefore, it should be possible to prepare 1,9-diacetamino-4,6-dimethoxydibenzofuran in excellent yield by diacetylating 4,6-dimethoxydibenzofuran followed by rearrangement of the corresponding dioxime. Hydrolysis would yield the 1,9-diamine. It would not be unreasonable to expect 1,9-diamino-4,6-dimethoxydibenzofuran to form an imidazole with aliphatic acids, thus bridging the 1- and 9-positions of the molecule.

Results of Physiological Tests. Ninety compounds containing a dibenzofuran nucelus have been submitted from this laboratory to be tested for analgesic action (16). An examination of the pharmacological data reveals that only two of the compounds, 4-aminodibenzofuran and the more complex 2-methyldibenzofuro-[2,3-d]-imidazole, have manifested significant analgesic activity. Paradoxically, 4,6-diamino-, 4-amino-6-methoxy-, 4-amino-6-hydroxy- and 1,2,3,4-tetrahydro-6-aminodibenzofuran elicited no observable analgesia in similar test animals (white mice and guinea pigs).

Eddy (128) has carefully compared the analgesic action of certain dibenzofuran derivatives with that manifested by phenanthrene analogs. He concluded that definite action can be elicited in cats with compounds containing the dibenzofuran nucleus. The

(128) Eddy, J. Pharmacol., 58, 159 (1936).

study showed that dibenzofuran derivatives are more analgesic but usually more toxic than their phenanthrene analogs.

Slight structural modifications in the morphine molecule profoundly alter its remarkable analgesic and addicting powers. Pukateine (129), a naturally occurring alkaloid which is reported to rival morphine in its power to alleviate pain, has yielded to synthetic attack (86). Although it bears a structural resemblance to morphine, the molecule is much less complex. Orientation and metalation studies applied to dibenzofuran have furnished the requisite knowledge for higher synthetic endeavor. Isoquinoline derivatives of 4-hydroxy- and 4,6-dihydroxydibenzofuran might elicit marked physiological activity. 4,5-Phenanthrylene oxides may yet evolve from a dibenzofuran origin. The significance of Ehrlich's "606" should dispel untimely discouragement. Available facts do not deny a predilection for the idea that the dibenzofuran nucleus is a good foundation on which to build the ideal, non-addicting meo-morphine of the future.

Parker (13) has published the pharmacological data pertaining to the first seventy-eight compounds of the HD series submitted from this laboratory to be examined for analgesic activity (16). Sixty-nine of these compounds were dibenzofuran derivatives, the other nine being derivatives of benzofuran, phenoxthin and dibenzothiophene. All additional compounds tested appear in Table II.

(129) Fogg, J. Pharmacol., 54, 167 (1935).

TABLE II

HD No.	NAME OF COMPOUND	M. L. D.* in mg. per g.
79	2-Methyl-8-acetyldibenzofuro-[2,3-d]-imidazole	0.6
80	9-Methylphenanthridine	0.25
81	2-Dimethylaminomethyl-1-keto-1,2,3,4-tetrahydrobrazan hydrochloride	0.20
82	2-Acetaminodibenzothiophene	0.15**
83	1-Acetamino-4-methoxydibenzofuran	0.10
84	4-Amino-6-methoxydibenzofuran	0.18
85	9-(β,β'-Dihydroxyisopropyl)-phenanthridine	0.4
86	1-Acetamino-3,4-dimethoxydibenzofuran	0.12
87	Tetrahydro-2-methyl-1-benzo-[2,3-f]-benzimidazole hydrochloride	0.35
88	1-Keto-1,2,3,4-tetrahydrothiobrazan	0.15
89	2-Aminodibenzothiophene	0.12
90	4-Methoxydibenzothiophene	———
91	4-Hydroxydibenzothiophene	0.20
92	Phenanthridine	———
93	1-Acetamino-4,6-dimethoxydibenzofuran	0.15
94	4,6-Diacetoxydibenzofuran	----
95	3,4-Diacetoxydibenzofuran	0.15

* M. L. D. refers to minimal lethal dose.
** Some hypnotic effect.

TABLE II (continued)

HD No.	NAME OF COMPOUND	M. L. D. in mg. per g.
96	3,4-Dihydroxydibenzofuran	0.20
97	1-Amino-4,6-dimethoxydibenzofuran hydrochloride	0.18
98	1-Ethoxalyl-4-methoxydibenzofuran	0.15*
99	4-Amino-6-hydroxydibenzofuran hydrochloride	0.20
100	2,8-Dihydroxydibenzofuran	0.15
101	2,8-Diacetoxydibenzofuran	0.18*
102	4-Aminodibenzothiophene	0.20
103	4,6-Diaminodibenzofuran	0.20
104	1-Amino-3,4-dimethoxydibenzofuran	0.06
105	3-Hydrazinodibenzofuran	0.03
106	2,8-Diaminodibenzofuran	0.40*

*Slight analgesic action.

S U M M A R Y

I. The amino and hydroxy derivatives of dibenzofuran have been tabulated.

II. The preparations of fifty amino and hydroxy derivatives of dibenzofuran have been described, and evidence for the assigned structures of these compounds has been presented.

III. Approaches to the bridging of the 1- and 9-positions in the dibenzofuran molecule have been discussed.

IV. The results of pharmacological tests involving derivatives of dibenzofuran, dibenzothiophene and phenanthridine have been listed.